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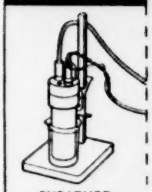

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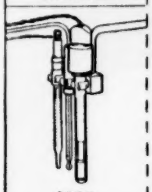

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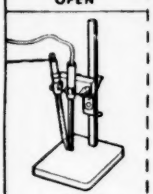

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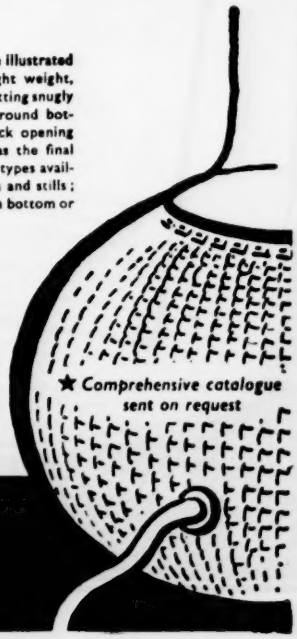

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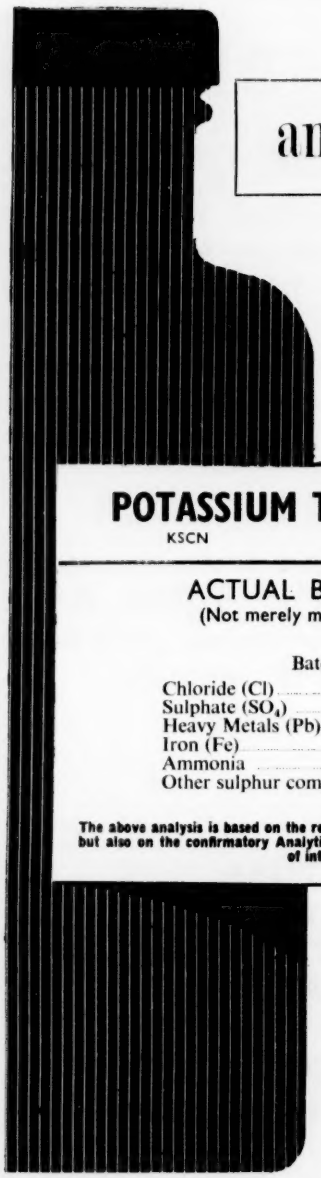

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404. *Oxidations with Phenyl Iodosoacetate. Part II.* The Oxidation of Primary Aromatic Amines.*

By K. H. Pausacker.

Some primary aromatic amines have been oxidised by phenyl iodosoacetate in benzene and the nature of some of the products has been examined.

Although primary aromatic amines have been oxidised with a number of different reagents, there is relatively little evidence concerning the effect of structure on the nature of the product. The only investigation of this nature is by Saunders *et al.* (see *J.*, 1951, 3433, for preceding references), who have investigated the action of hydrogen peroxide, catalysed by the enzyme peroxidase, on several primary aromatic amines. In the present work, fifteen primary aromatic amines have been oxidised by phenyl iodosoacetate in benzene solution.

In preliminary experiments, the amine (*ca.* 5×10^{-4} mole) and phenyl iodosoacetate (*ca.* 15×10^{-4} mole) were dissolved in dry benzene (25 ml.) and 1-ml. aliquots were withdrawn daily and titrated with *ca.* 0·05N-sodium thiosulphate after the addition of acidified potassium iodide. In addition, it was found that characteristic colours were obtained when *ca.* 1 mg. of amine was added to 2 ml. of a 1% solution of phenyl iodosoacetate in glacial acetic acid. The results are in Table 1.

Table 1.

Compound	$PhI(OAc)_2$ consumed (mol.)	Days reqd. for completion	Immediate colour	Colour after 1 hr.
Aniline	1·92	2	Transient purple, then deep green, becoming brown	Dark brown
o-Toluidine	1·62	2	Purple, becoming mauve	Deep carmine
m- ,,	1·58	1	Transient pink, then dark brown	Dark brown
p- ,,	1·94	1	Light brown	Light brown
o-Chloroaniline	1·51	4	Pale brown	Light brown
m- ,,	1·13	1	Wine-red	Deep red-brown
p- ,,	1·62	2	Pink	Red
o-Anisidine	1·67	2	Dark brown	Dark brown
p- ,,	1·56	1	Purple slowly appearing	Deep carmine
o-Nitroaniline	1·16	2	Yellow	Yellow
m- ,,	1·05	2	Yellow	Light brown
p- ,,	1·16	2	Yellow	Dark yellow
α-Naphthylamine	1·60	1	Blue green, rapidly becoming brown	Light brown
β- ,,	1·89	1	Light brown	Red brown

When the amines were treated with phenyl iodosoacetate, in the ratios shown, the corresponding azo-compounds were the only products that could be isolated from the following (percentage yields in parentheses): aniline (95); *o*-toluidine (42); *m*-toluidine (56); *p*-toluidine (6); *o*-chloroaniline (39); *m*-chloroaniline (66); *p*-chloroaniline (55); *o*-anisidine (3); *m*-nitroaniline (65); *p*-nitroaniline (53); and α-naphthylamine (3).

When *o*-nitroaniline was oxidised, benzofurazan oxide was formed in 81% yield. Green and Rowe (*J.*, 1912, **101**, 2449) have reported that *o*-nitroaniline is converted into benzofurazan oxide by alkaline sodium hypochlorite but into the corresponding azo-compound under neutral conditions (*J.*, 1912, **101**, 2455). Similarly, phenyl iodosoacetate converted 4-methyl- and 4-chloro-2-nitroaniline and 2 : 4-dinitroaniline into the corresponding benzofurazan oxides in yields of 96%, 91%, and 94% respectively.

β-Naphthylamine is oxidised to 1 : 2 : 6 : 7-dibenzophenazine (28%) and a product, $C_{25}H_{20}O_5N_2$, which has a green metallic lustre, gives a deep blue solution in nitrobenzene, and resembles that obtained by Liebermann (*Annalen*, 1876, **183**, 265) on oxidation of β-naphthylamine by ferric chloride. 1 : 2 : 6 : 7-Dibenzophenazine has previously been

* Part I is considered to be "The Oxidation of Glycols by Aryl Iodosoacetates," *J.*, 1953, 107.

obtained (Claus and Jaeck, D.R.-P. 78,748) by the oxidation of β-naphthylamine with calcium hypochlorite.

Although *p*-anisidine and *p*-phenetidine were converted into the azo-compounds in yields of 5% and 7% respectively, several other compounds could be isolated. The products from *p*-anisidine differed from those reported by Daniels and Saunders (*J.*, 1951, 2112). A study of the oxidation of alkoxy- and aryloxy-amines will be reported later.

Pausacker (*loc. cit.*) suggested that the azo-compounds are formed as follows:

$$2PhI(OAc)_2 + 2Ar{\cdot}NH_2 \rightleftharpoons 2PhI(OAc){\cdot}NHAr + 2AcOH$$

$$2PhI + 2AcOH + Ar{\cdot}N{:}N{\cdot}Ar \leftarrow 2PhI(OAc){\cdot} + Ar{\cdot}NH{\cdot}NH{\cdot}Ar \leftarrow 2Ar{\cdot}NH{\cdot} + 2PhI(OAc){\cdot}$$

Partial confirmation comes in oxidation of hydrazobenzene to azobenzene in 92% yield by phenyl iodosoacetate. This type of free-radical mechanism can also be extended to explain the formation of 1 : 2 : 6 : 7-dibenzophenazine from β-naphthylamine and of benzofurazan oxide from *o*-nitroaniline.

Experimental

Analyses are by Dr. W. Zimmermann.

The amount of phenyl iodosoacetate indicated in Table 1 was dissolved in dry thiophen-free benzene (30 ml. per g.), and the amine (*ca.* 1—2 g.) added. After the required time at room temperature, the solution was concentrated and chromatographed on alumina, with benzene as eluant. The azo-compound (or benzofurazan oxide) was in the bottom band. Azobenzene was identified by m. p. (68°) and mixed m. p. The m. p.s and analyses of the other azo-compounds are in Table 2.

Table 2.

Substituents in azobenzene	M. p. found	M. p. lit.	Solvent	Found (%): C	Found (%): H	Found (%): N	Calc. (%): C	Calc. (%): H	Calc. (%): N
2 : 2′-Me_2	52°	55°	Ethanol	—	—	12·9	—	—	13·3
3 : 3′-Me_2	50	55	Methanol	—	—	13·2	—	—	—
4 : 4′-Me_2	142	143	Ethanol	—	—	13·0	—	—	—
2 : 2′-Cl_2	136	137	Benzene	57·1	3·2	10·8	57·5	3·2	11·15
3 : 3′-Cl_2	103	101	,,	57·5	3·3	10·9	—	—	—
4 : 4′-Cl_2	184	184	,,	57·4	3·4	10·8	—	—	—
3 : 3′-$(NO_2)_2$	152	153	*cyclo*Hexane	53·2	3·0	21·0	52·95	2·9	20·6
4 : 4′-$(NO_2)_2$	219	220	Benzene	53·0	2·9	21·0	—	—	—
2 : 2′-$(OMe)_2$	154	153	Methanol	—	—	11·5	—	—	12·0
4 : 4′-$(OMe)_2$	163	164	,,	—	—	11·6	—	—	—
4 : 4′-$(OEt)_2$	160	160	Ethanol	71·5	7·1	10·4	71·1	6·7	10·4
1 : 1′-Azonaphthalene	190	190	Light petroleum (b. p. 80—100°)	85·3	5·0	9·9	85·1	5·0	9·9

Table 3 summarises the data for the products formed on oxidation of the *o*-nitroanilines and crystallised from light petroleum (b. p. 40—60°).

Substituent in benzofurazan oxide	M. p. found	M. p. lit.	Found (%): C	Found (%): H	Found (%): N	Calc. (%): C	Calc. (%): H	Calc. (%): N
—	70°	72°	53·5	3·1	20·2	53·0	2·9	20·6
5-Cl	48	48	42·5	2·0	—	42·2	1·8	—
5-NO_2	67	72	39·9	1·7	—	39·9	1·7	—
5-Me	96	97	56·3	4·0	19·1	56·0	4·0	18·7

Oxidation of β-Napthylamine.—β-Naphthylamine (1·40 g.) was added to phenyl iodosoacetate (6·7 g.) in dry thiophen-free benzene (200 ml.). After 2 days at room temperature, the solution was filtered, yielding a compound (0·92 g.) with a green metallic lustre. This was insoluble in most organic solvents and could only be crystallised from nitrobenzene in which it formed a deep blue solution; it had m. p. >300° (Found: C, 69·8, 69·6; H, 4·4, 4·4; N, 6·6, 6·5. Calc. for $C_{25}H_{20}O_5N_4$: C, 70·0; H, 4·7; N, 6·5%). The initial filtrate was concentrated and chromatographed on alumina. A red band was obtained which yielded 1 : 2 : 6 : 7-dibenzophenazine (0·40 g.; m. p. 286°; lit. m. p. 284°) after crystallisation from benzene (Found: C, 85·3; H, 4·3; N, 10·1. Calc. for $C_{20}H_{12}N_2$: C, 85·7; H, 4·3; N, 10·0%).

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[*Received, February 2nd*, 1953.]

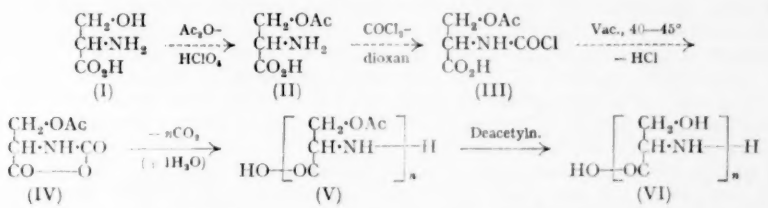
405. *Synthesis of Poly-(O-acetyl-DL-serine) and of Poly-DL-serine.*

By MAX FRANKEL, (MRS.) S. CORDOVA, and M. BREUER.

O-Acetyl-*N*-carboxy-DL-serine anhydride (IV) has been prepared by direct action of carbonyl chloride on *O*-acetyl-DL-serine. Polymerisation of the anhydride by heat in a high vacuum, or at room temperature in solution and in the presence of initiators, gives poly-(*O*-acetyl-DL-serine) (V), and by subsequent treatment with ammonia poly-DL-serine (VI). The average chain length of the polymers described varied from 10 to 45 units.

THE preparation of the *N*-carboxy-anhydrides of *O*-acetyl- and *O*-carbobenzyloxy-DL-serine, through *O*-acetyl-*N*-carbobenzyloxy- and *ON*-dicarbobenzyloxy-DL-serine respectively, was described by Frankel and Halman (*J.*, 1952, 2735). With the aid of these anhydrides the synthesis of poly-(*O*-acetyl-DL-serine) and poly-DL-serine is possible in principle, but some of the features of the preparative procedure made a different route desirable (cf. Frankel, Breuer, and Cordova, *Experientia*, 1952, **8**, 299; Breuer, Thesis, Hebrew University, Jerusalem, 1950—51).

Frankel and Halman's preparation of *O*-acetyl-*N*-carboxy-DL-serine anhydride involves isolation of *N*-carbobenzyloxy-DL-serine, its acetylation, chlorination, and subsequent ring closure. This procedure can be greatly simplified. Acetylation of only the hydroxyl group of DL-serine (I) can be realized by using perchloric acid and acetic anhydride in glacial acetic acid (cf. Sakami and Toennies, *J. Biol. Chem.*, 1942, **144**, 203), which leads to *O*-acetyl-DL-serine (II). By direct action of carbonyl chloride on a suspension of (II) in dioxan under the conditions described in the Experimental section, *O*-acetyl-*N*-carboxy-DL-serine anhydride (IV) was obtained directly. The intermediate *N*-substituted chloride (III) is decomposed during the treatment, with loss of hydrogen chloride. This procedure is an extension to a polyfunctional α-amino-acid of the findings of previous authors (Fuchs, *Ber.*, 1922, **55**, 2943; Levy, *Nature*, 1950, **165**, 152; Farthing and Reynolds, *ibid.*, p. 647, who cite patent literature; Farthing, *J.*, 1950, 3213) who have shown that anhydro-*N*-carboxy-derivatives of the type (IV) can be obtained directly by the action of carbonyl chloride on certain simple bifunctional α-amino-acids.



Polymerisation of the anhydride (IV) was effected by heat in a high vacuum, near the decomposition temperature, as in previous cases (cf. Frankel and Berger *J. Org. Chem.*, 1951, **16**, 1513 for earlier references), or in solution. Dioxan, nitrobenzene, or pyridine served as solvents; in the first case, at room temperature, water or sodium hydroxide was used as initiator (Coleman and Farthing, *J.*, 1950, 3218; Coleman, *ibid.*, p. 3222), or the dioxan solutions were heated. With nitrobenzene as solvent, glycine dimethylamide was the initiator (Hanby, Waley, and Watson, *J.*, 1950, 3009; Coleman, *loc. cit.*).

Poly-(*O*-acetyl-DL-serine) (V) thus obtained was soluble in hot glacial acetic acid and precipitated from solution on addition of dry ether. The biuret reaction was strongly and the ninhydrin reaction weakly positive. The average chain length varied, depending on the conditions of the polymerisation, from about 10 to about 45 units, as deduced from analytical data, including amino-nitrogen values determined by van Slyke's manometric method.

Complete removal of the acetyl groups from the poly-(*O*-acetyl-DL-serine) without hydrolysis of peptide bonds presented difficulties. On the one hand, the quantitative

removal of the acetyl group was not easily accomplished and, on the other, it became apparent in our experiments, that the peptide bonds in the poly-DL-serine preparations are very readily hydrolysed even under mild conditions. Thus, *e.g.*, an aqueous solution of poly-DL-serine which was brought to pH 8—9 by addition of sodium hydroxide and then kept at 30° for 2 hr., showed an increase in amino-nitrogen content from 0·59 to 1·75%, corresponding to a degradation from an average chain length of 27 to one of 9 units. After a further hour, the amino-nitrogen content was 2%. Similar observations were frequently made in our experiments, and are in agreement with recent findings that a peptide linkage adjacent to a hydroxyl group undergoes hydrolysis in acid or alkaline medium much more easily than in absence of such hydroxyl groups (Desnuelle and Casal, *Biochem. Biophys. Acta*, 1948, **2**, 64; *Chem. Abs.*, 1949, **43**, 2943; Sanger, *Adv. Protein Chem.*, 1952, **7**, 18—24). Removal of the acetyl groups from poly-(*O*-acetyl-DL-serine) was attempted with barium or lithium hydroxide, with alkoxide solutions, and with ammonia. Finally, concentrated aqueous ammonia was found completely effective, practically without hydrolysis of the peptide bonds. The acetamide and ammonium acetate formed were removed by extraction with alcohol, followed by vacuum-sublimation.

Poly-DL-serine is hygroscopic, easily soluble in water, and gives strong ninhydrin and biuret reactions. From its aqueous solutions, on evaporation, hard films are obtained.

Hydrolysis of poly-(*O*-acetyl-DL-serine) and of poly-DL-serine by boiling hydrochloric acid (18 hr.) was practically quantitative, yielding DL-serine. In the former case the product sometimes contained *O*-acetyl-DL-serine which was detected by paper chromatography.

Infra-red absorption spectra of poly-DL-serine and of poly-(*O*-acetyl-DL-serine) were kindly measured out by Dr. Sadtler and are consistent with the constitutions assigned. They will appear in Sadtler's "Catalog of Infra-red Spectrograms," Philadelphia.

Experimental

M. p.s were determined in a Fisher–Johns apparatus.

DL-Serine (Merck, Rahway, U.S.A.), used in these experiments, showed m. p. 228° (decomp.) (Found: amino-N, 13·2. Calc. for $C_3H_7O_3N$: amino-N, 13·3%).

O-Acetyl-DL-serine (cf. Sakami and Toennies *loc. cit.*).—The acetylation mixture was prepared from perchloric acid (60·4%; 4·99 g.) and acetic anhydride (98·7%; 2·52 g.), made up to 50 ml. with acetic acid (100%; prepared from glacial acetic acid and acetic anhydride). To a solution of DL-serine (2·5 g.) in this mixture, at 0°, acetic anhydride (98·7%, 12 g.) was added. After 1½ hr. water (1 ml.) and then amylamine (3·48 g.) were added. *O*-Acetyl-DL-serine (3·1 g., 91%) was precipitated by ether (300 ml.). It was dried for 2 days in a vacuum-desiccator over solid sodium hydroxide and had m. p. 144° (decomp.) [Sakami and Toennies, *loc. cit.*, give m. p. 143—144° (decomp.)].

O-Acetyl-N-carboxy-DL-serine Anhydride.—A stream of dry carbonyl chloride was passed through a suspension of finely ground *O*-acetyl-DL-serine (7·5 g.) in dried dioxan (150 ml.), with exclusion of water, in a ground-glass apparatus, under a reflux condenser, and with stirring, at 40—48° (bath). Within 1½ hr. the *O*-acetyl-DL-serine dissolved entirely. Passage of carbonyl chloride was continued for a further ½ hr.; the solution was then filtered, excess of carbonyl chloride removed *in vacuo* at room temperature, and the dioxan distilled off at the water-pump at 40—45° (bath). The remaining oil was left overnight in a vacuum-desiccator over phosphoric oxide. It was used directly for the following polymerisation reactions.

Polymerisation Experiments.—Dioxan was dried over sodium. Where necessary, moisture was excluded by calcium chloride.

(a) *Polymerisation in a high vacuum.* *O*-Acetyl-*N*-carboxy-DL-serine anhydride (1·5 g.) was heated gradually at an initial pressure of 0·04 mm. Within 1 hr., the bath temperature reaching 50°, a slight evolution of gas occurred, causing a rise in pressure to 1 mm. The temperature was gradually raised as gas evolution ceased; after another 45 min., at 86°, a strong evolution of gas began which lasted for 1 hr., the temperature reaching 108°. At this point the substance hardened at once. The pressure, which during the strong evolution of gas increased considerably, dropped to the initial value, and heating to 125° caused no visible change. The substance was kept overnight in the high-vacuum system. It was soluble in cold dichloroacetic acid and formamide, and only slightly in hot glacial acetic acid. It was dissolved in formamide,

precipitated by absolute alcohol, and washed three times with absolute alcohol, being separated each time by centrifugation.

Poly-(O-acetyl-DL-serine) thus obtained (700 mg.) was yellowish, slightly soluble in hot glacial acetic acid, giving a strong biuret and a weak ninhydrin reaction. The average chain length was 45 units [Found: C, 45·9; H, 5·5; N, 10·4; amino-N, 0·24. $(C_5H_7O_3N)_{45},H_2O$ requires C, 46·4; H, 5·4; N, 10·8; amino-N, 0·24%].

(b) *Polymerisation in solution.* With dioxan as solvent small amounts of water or sodium hydroxide solution were used as initiators at room temperature, or, alternatively, the solution was heated without initiator. Precipitates of poly-(*O*-acetyl-DL-serine) were filtered off and submitted to ether-extraction (Soxhlet) or first dissolved in hot glacial acetic acid, reprecipitated by ether, and freed from acetic acid by ether-extraction (Soxhlet). Glacial acetic acid was also used to fractionate some of the polymer preparations (cf. Table).

In the case of nitrobenzene, glycine dimethylamide was the initiator, and the polymer was precipitated by absolute alcohol.

When pyridine was used, water present in traces might have acted as initiator. In this case the polymerisation led to gel formation. Glacial acetic acid was added and the polymer precipitated by dry ether.

The poly-(*O*-acetyl-DL-serine) preparations thus obtained constituted white, in some instances (when obtained by heat-polymerisation) yellowish to brown, substances, with a tendency to form films from solution; they gave weak ninhydrin and strong biuret reactions. As in other cases with polymeric polypeptides (cf., *e.g.*, Hanby, Waley, and Watson, *J.*, 1950, 3009), C and H determinations were not always satisfactory.

The polymerisation experiments in solution are summarised in the Table.

Expt.	Anhydride (g.)	Solvent (ml.)	Mode of polymern.	Time of polymern. (days)	Average degree of polymern. (*n*)
1	4·5	Dioxan (45)	One drop of water as initiator at room temp.[a]	10	9
2	11·4	Dioxan (60)	Three drops of 0·5% sodium hydroxide as initiator at room temp.[b]	15	17 35[c]
3	3·1	Dioxan (20)	Heat on water-bath under reflux	35 hr.	35
4	2·0	Pyridine (6)	Room temp.	2	17
5	3·0	$PhNO_2$ (20)	0·01 ml. of glycine dimethylamide as initiator	14	?[d]

Expt.	Found (%): C	H	Total N	Amino-N	Reqd. for $(C_5H_7O_3N)_n,H_2O$: C	H	Total N	Amino-N
1	43·5	6·3	10·6	1·2	45·8	5·5	10·7	1·18
2	—	—	9·1	0·63	—	—	10·8	0·63
	43·9	5·3	10·0	0·31	46·3	5·4	10·8	0·31
3	—	—	10·2	0·31	—	—	10·8	0·31
4	—	—	10·1	0·64	—	—	10·8	0·63
5	44·3	5·6	10·0	—	46·5	5·4	10·8	—

[a] The small amount of ppt. formed on addition of water was removed by centrifugation.
[b] One drop of the sodium hydroxide solution was added in the first instance. Since for 14 days no precipitate was formed, two additional drops were added.
[c] By dissolving the initial ppt. in hot glacial acetic acid and reprecipitating it by ether, a polymer having an average degree of polymerisation $n = 35$ was obtained.
[d] This polymer was not soluble in any suitable solvent and amino-nitrogen analyses could therefore not be carried out.

Deacetylation of Poly-(O-Acetyl-DL-serine) by Ammonium Hydroxide Solution.—Poly-(*O*-acetyl-DL-serine) ($n = 35$; 0·5 g.) was added to a solution of aqueous ammonia (28%; 5 ml.). Within 2 hr. a clear solution was obtained which was left at room temperature for 3 days. The ammonia was then removed in a stream of air at room temperature, and then the water entirely evaporated in a vacuum-desiccator over concentrated sulphuric acid. In order to remove quantitatively acetamide and the ammonium acetate formed, the remaining residue was extracted with hot alcohol (Soxhlet) and then sublimed at 75°/3—5 mm. The residual *poly-DL-serine* constituted a white hygroscopic substance, soluble in water, acetic acid, or dilute aqueous alkali. The last solvent causes considerable hydrolysis of the peptide linkages even in the cold. The average degree of polymerisation was 35 [Found: C, 40·7; H, 6·3; N, 15·8; amino-N, 0·45. $(C_5H_9O_2N)_{35},H_2O$ requires C, 41·1; H, 5·8; N, 16·0; amino-N, 0·45%].

Complete Hydrolysis of Poly-(O-acetyl-DL-serine) and of Poly-DL-serine.—Solutions of poly-(*O*-acetyl-DL-serine) (obtained by polymerisation in dioxan with sodium hydroxide as initiator; $n = 35$; 55·3 mg.), of poly-(*O*-acetyl-DL-serine) (obtained by polymerisation in hot dioxan; $n = 35$; 57·0 mg.), and of poly-DL-serine ($n = 27$; 43·6 mg.) in hydrochloric acid (17·5%;

each in 4 ml.) were refluxed for 18 hr., then neutralised by lithium hydroxide (*ca.* 5N) (methyl-orange) and brought to 25 ml. with water. In aliquot parts of the solutions total and amino-nitrogen were determined (they were practically identical and indicated complete hydrolysis). Parts of the solutions were evaporated to dryness *in vacuo* and the remaining solids extracted by ether or acetone, to remove lithium chloride. The residue which still gave lithium- and chloride-ion reactions was submitted to short-path distillation. In the sublimate, DL-serine was identified by the m. p. and mixed m. p.

The above hydrolysates were submitted to paper partition chromatography, along with the DL-serine, *O*-acetyl-DL-serine, and poly-DL-serine, by the ascending method with phenol–water as mobile phase. On development with ninhydrin, the three hydrolysates yielded spots identical with that found for the DL-serine. The second hydrolysate gave an additional spot identical with that given by *O*-acetyl-DL-serine. Poly-DL-serine yielded no spot. Poly-(*O*-acetyl-DL-serine) could not be tested owing to its insolubility in water.

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406. *The Reactions of Certain Nitrogen-containing Compounds derived from Benzotrifluoride.*

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Diazotised *m*-aminobenzotrifluoride with dimethylaniline, phenol, and β-naphthol, gave the expected azo-compounds, and with the parent amine gave 3 : 3′-bistrifluoromethyldiazoaminobenzene which could not be rearranged. 3 : 3′-Bistrifluoromethylazobenzene gave the azoxy-compound on oxidation, and, when treated with sodium amalgam and then with mineral acids, afforded 2 : 2′-bistrifluoromethylbenzidine. 2 : 2′-Bistrifluoromethylhydrazobenzene was fairly stable; it was converted into the corresponding benzidine derivative under drastic conditions.

THIS paper describes the application of certain classical reactions to some nitrogenous aromatic compounds containing trifluoromethyl groups. *m*-Aminobenzotrifluoride (Swarts, *Bull. Acad. roy. Belg.*, 1898, [iii], **35**, 375) was diazotised in the usual way and was coupled with phenol, β-naphthol, and dimethylaniline to give the expected azo-compounds. The structure of that derived from the tertiary amine was confirmed by reductive cleavage and acetylation of the fragments; this azo-compound has been mentioned by Miller, Sapp, and Miller (*Cancer Research*, 1949, **9**, 652). Diazotisation and self-coupling of *m*-aminobenzotrifluoride proceeded readily in the absence of an excess of mineral acid, the structure of the product, 3 : 3′-bistrifluoromethyldiazoaminobenzene, being proved by hydrogenolysis to ammonia and the parent amine. This diazoamino-compound could not be rearranged to the aminoazo-product; unless complete decomposition was induced, the starting material was recovered. The diazoamino-structure is stabilised, evidently, by the presence of trifluoromethyl substituents, and the recovery of the starting material from an attempted rearrangement in the presence of acid and dimethylaniline suggests that initial rupture of the nitrogen chain is difficult.

3 : 3′-Bistrifluoromethylazobenzene was first made by Swarts (*Bull. Acad. roy. Belg.*, 1922, **8**, 343) as a by-product of the oxidation of *m*-aminobenzotrifluoride with chromic acid; Gonze (*Bull. Soc. chim. Belg.*, 1934, **43**, 504; *Bull. Acad. roy. Belg.*, 1934, **20**, 809) prepared from it the corresponding hydrazo-compound which was somewhat less easily oxidised than the analogous toluene derivative. Gonze found that the hydrazo-compound did not readily undergo the benzidine transformation, 10% hydrochloric acid giving mainly a mixture of the parent amine and azo-compound, though a small amount of unidentified solid was isolated also. We prepared 3 : 3′-bistrifluoromethylazobenzene by reduction of *m*-nitrobenzotrifluoride, either with zinc dust and sodium hydroxide (*idem*, *loc. cit.*), or electrolytically. Oxidation of the azo-compound with hydrogen peroxide–acetic acid

afforded the analogous azoxy-derivative, of which the structure was confirmed by reduction to *m*-aminobenzotrifluoride. Reduction of the 3 : 3′-azo-compound, in alcohol, by sodium amalgam gave a colourless solution containing Gonze's hydrazo-compound. When this solution was added directly to warm sulphuric acid (50% by volume), there were obtained, after removal of the regenerated azo-compound, two bases, m. p. 180—182° and 141° (conversions of 11% and 1·5%) respectively, each of which had a correct analysis for a diaminobistrifluoromethyldiphenyl. The product having m. p. 180—182° was shown to be the benzidine derivative, 4 : 4′-diamino-2 : 2′-bistrifluoromethyldiphenyl, since, after tetrazotisation, and reduction with hypophosphorous acid, 2 : 2′-bistrifluoromethyldiphenyl was obtained, as was shown by its conversion with hot sulphuric acid (Le Fave's process, *J. Amer. Chem. Soc.*, 1949, **71**, 4148) into 9-oxofluorene-4-carboxylic acid, which is known to be formed from diphenic acid, the expected primary product, under these conditions (Graebe and Aubin, *Ber.*, 1887, **20**, 845). Complete proof of the structure of the benzidine was afforded by its identity with the product obtained by Pettit and Tatlow (*J.*, 1951, **3459**) *via* an Ullmann reaction upon 2-iodo-5-nitrobenzotrifluoride. The second product, m. p. 141°, is as yet unidentified, though, from the usual course of rearrangements of hydrazobenzenes, it may well be 2 : 4′-diamino-4 : 2′-bistrifluoromethyldiphenyl. In this particular benzidine transformation, disproportionation occurs to a considerable extent, confirming Gonze's original conclusions (*loc. cit.*).

Electrolytic reduction of *o*-nitrobenzotrifluoride gave 2 : 2′-bistrifluoromethylazobenzene, which, with sodium amalgam, afforded 2 : 2′-bistrifluoromethylhydrazobenzene which by hydrogenolysis gave *o*-aminobenzotrifluoride. The 2 : 2′-bistrifluoromethyl derivative is relatively stable for a hydrazo-compound; it was not, apparently, oxidized appreciably in air, and was recovered after treatment with dilute mineral acids under conditions which cause rearrangements of many hydrazo-compounds. More concentrated sulphuric acid (2 : 1 H_2SO_4–H_2O by vol.), however, did effect a transformation. A small amount of 2 : 2′-bistrifluoromethylazobenzene was formed, but the main product was 4 : 4′-diamino-3 : 3′-bistrifluoromethyldiphenyl: this and its bistrifluoroacetyl derivative were identical with the compounds prepared by Pettit and Tatlow (*loc. cit.*) through an Ullmann reaction on 5-iodo-2-nitrobenzotrifluoride.

It appears that trifluoromethyl substituents in aromatic nuclei hinder the two types of acid-catalysed transformations considered in this investigation. The conversion of a diazoamino- into an aminoazo-compound is usually thought to proceed intermolecularly, following reaction with a proton (cf. Hughes and Ingold, *Quart. Reviews*, 1952, **6**, 34), and the benzidine transformation intramolecularly, after addition of two protons to the hydrazo-derivative (*idem*, *loc. cit.*; Hammond and Shine, *J. Amer. Chem. Soc.*, 1950, **72**, 220). Presumably the presence of trifluoromethyl groups causes proton additions to proceed less readily than with unsubstituted compounds. Though there are few reports of the effect it appears that the presence of other electrophilic substituents hinders these rearrangements, since Zettel (*Ber.*, 1893, **26**, 2471) found that tetrachlorodiazoaminobenzene was unusually stable to acids, and Carlin and Forshey (*J. Amer. Chem. Soc.*, 1950, **72**, 793) had to use drastic conditions to effect transformations of 3 : 3′ : 5 : 5′-tetrachloro- and -bromohydrazobenzene (see also Meyer, Meyer, and Taeger, *Ber.*, 1920, **53**, 2034), steric effects not being the complete explanation. Similar stability is shown by 2 : 2′-dichloro- (Dey, Govindachari, and Rajagopalan, *J. Sci. Ind. Res., India*, 1946, **4**, 645) and 2 : 2′ : 5 : 5′-tetrachloro-hydrazobenzene (*idem*, *ibid.*, 1946, **5**, *B*, 75). Though trifluoromethyl substituents will reduce the basicity of the >NH groups, the actual reactions of protons with the latter may not be the rate-determining steps in these transformations. However, 2 : 2′-bistrifluoromethylhydrazobenzene apparently did not form salts with acids at all readily.

Experimental

Coupling of Diazotised m-*Aminobenzotrifluoride with Dimethylaniline.*—*m*-Aminobenzotrifluoride (5·00 g.) was warmed with concentrated hydrochloric acid (7·8 c.c.) and water (7·8 c.c.) to give a solution which was stirred mechanically and cooled to 0° whilst sodium nitrite (2·25 g.) in water (10·0 c.c.) was added, followed by dimethylaniline (3·76 g.) in hydrochloric acid (5·8 c.c; 6N), and sodium acetate (5·0 g.) in water (12·0 c.c.). The resultant precipitate was washed and

recrystallised, first from ethyl alcohol made very slightly alkaline with aqueous potassium hydroxide, and then from light petroleum (b. p. 60—80°), to give orange-red 4-dimethylamino-3′-trifluoromethylazobenzene (3·98 g.), m. p. 81—82° (Found: C, 61·5; H, 5·0; F, 18·8. Calc. for $C_{15}H_{14}N_3F_3$: C, 61·4; H, 4·8; F, 19·4%). Miller, Sapp, and Miller (*loc. cit.*) gave m. p. 77—79°.

This azo-compound (2·00 g.), Raney nickel (*ca.* 0·5 g.), and ethyl alcohol (25·0 c.c.) were shaken together in hydrogen until absorption (325 c.c.) was complete (80 min.). After filtration and evaporation, the product was distilled *in vacuo*, to give a fraction (a), b. p. 115—160° (bath)/17 mm., and a residue (b). Fraction (a), acetic acid (1·0 c.c.), and acetic anhydride (1·2 c.c.) were heated to 100° for 3 min., to give, after isolation as usual, *m*-acetamidobenzotrifluoride (1·07 g.), m. p. and mixed m. p. 104°, for which Swarts (*loc. cit.*, 1898) gave m. p. 103°. The residue (b), after similar treatment, afforded, after two recrystallisations of the product from water, *p*-acetamido-*NN*-dimethylaniline (0·18 g.), m. p. and mixed m. p. 128—130°.

Coupling of Diazotised m-*Aminobenzotrifluoride with Phenol and with* β-*Naphthol.*—(*a*) The amine (2·50 g.), in water (12 c.c.) and concentrated hydrochloric acid (3·9 c.c.), was diazotised at 0° with sodium nitrite (1·13 g.), in water (5 c.c.), and the solution was treated with phenol (1·60 g.), in aqueous sodium hydroxide, the solution being made slightly alkaline. The precipitate, after being washed, dried, and recrystallised from carbon tetrachloride, gave yellow 4-*hydroxy*-3′-*trifluoromethylazobenzene* (2·91 g.), m. p. 110—111° (Found: C, 58·5; H, 3·4; F, 21·1. $C_{13}H_9ON_2F_3$ requires C, 58·65; H, 3·4; F, 21·4%).

(*b*) A similar reaction in which the amine was diazotised and coupled with β-naphthol at pH 7—8 afforded, after recrystallisation from ethyl alcohol, the red 3-*trifluoromethylphenylazo*-β-*naphthol* (60%), m. p. 165—166° (Found: C, 64·7; H, 3·2; F, 17·8. $C_{17}H_{11}ON_2F_3$ requires C, 64·5; H, 3·5; F, 18·0%).

Diazotisation and Self-coupling of m-*Aminobenzotrifluoride.*—(*a*) The amine (3·22 g.), concentrated hydrochloric acid (2·6 c.c.), and water (5·2 c.c.) were warmed together until homogeneous, and then stirred mechanically and cooled to 0—5°. Sodium nitrite (0·72 g.) in water (5·0 c.c.) was added dropwise, followed by sodium acetate (3·0 g.) in water (6·0 c.c.), and after 10 min. the precipitate was removed, washed, and dried. Recrystallisation from light petroleum (b. p. 60—80°) afforded yellow 3 : 3′-*bistrifluoromethyldiazoaminobenzene* (2·67 g.), m. p. 117—118° (Found: C, 50·5; H, 2·8; F, 33·9. $C_{14}H_9N_3F_6$ requires C, 50·5; H, 2·7; F, 34·2%).

(*b*) (By Earl's process, *Chem. and Ind.*, 1936, **55**, 192.) *m*-Aminobenzotrifluoride (5·0 g.), saponin (0·1 g.), potassium chromate (0·2 g.), sodium nitrite (1·2 g.), and water (50 c.c.) were shaken together mechanically in an atmosphere of carbon dioxide (12″ Hg pressure) for 1 hr. The precipitate, after recrystallisation from *n*-hexane, had m. p. and mixed m. p. 117—118° (yield 3·25 g.).

(*c*) This diazoamino-compound was unaffected when heated with *m*-aminobenzotrifluoride and its hydrochloride, with the amine and hydrogen chloride in methyl alcohol, with concentrated hydrochloric acid, with dimethylaniline and a little concentrated hydrochloric acid, or with acetic acid or trifluoroacetic acid, alone or containing the parent amine, except that prolonged heating caused decomposition.

Reduction of 3 : 3′-*Bistrifluoromethyldiazoaminobenzene.*—This material (2·90 g.), light petroleum (30 c.c., b.p. 60—80°), and Raney nickel (*ca.* 2 g.) were shaken for 6 hr. at 130—140° in a rocking autoclave in hydrogen (120 atm.). Ammonia was present at the end of the reaction. After filtration of the product, a little concentrated hydrochloric acid was added to the filtrate, the petroleum was evaporated *in vacuo*, and the residual salt was taken up in water, diazotised, and coupled with β-naphthol as described before, to give 3-trifluoromethylphenylazo-β-naphthol (3·21 g.), m. p. and mixed m. p. 165°.

3 : 3′-*Bistrifluoromethylazobenzene from* m-*Nitrobenzotrifluoride.*—The apparatus comprised a cylindrical porous pot, which carried a sheet-lead anode (*ca.* 110 sq. cm.), was filled with saturated aqueous sodium carbonate, and was contained in a beaker (capacity 1 l.) which held also a lead cathode (*ca.* 110 sq. cm.) To the cathode compartment were added *m*-nitrobenzotrifluoride (35·8 g.), ethyl alcohol (350 c.c.), water (30 c.c.), and sodium acetate (10 g.). The cathode solution was stirred mechanically, and current was passed (at 12 v, this rose to 10 amp. after 1 hr.; the voltage was then reduced progressively to 7 to keep the amperage at 10) until appreciable evolution of hydrogen occurred (*ca.* 2½ hr.). The temperature rose to about 60° during the reaction, a little alcohol being added to the cathode compartment and water to the anode compartment to replace losses. Air was drawn through the cathodic solution for 20 min., and the deposited solid was washed and recrystallised from aqueous alcohol, affording

red **3** : 3′-bistrifluoromethylazobenzene (17·3 g.), m. p. 82° (Found : C, 52·9; H, 2·6; F, 35·6. Calc. for $C_{14}H_8N_2F_6$: C, 52·8; H, 2·5; F, 35·8%), for which Swarts (*loc. cit.*, 1922) gave m. p. 82·3°.

3 : 3′-*Bistrifluoromethylazoxybenzene*.—**3** : 3′-Bistrifluoromethylazobenzene (2·00 g.), acetic acid (75 c.c.), and hydrogen peroxide solution (10 c.c., 100-vol.) were heated at 80° for 20 hr., further portions of hydrogen peroxide (3 × 5 c.c.) being added at intervals of 5 hr. The solution was poured into excess of water and the precipitate was washed and recrystallised from aqueous ethyl alcohol, to give **3 : 3′-*bistrifluoromethylazoxybenzene*** (1·82 g.), m. p. 47° (Found : C, 50·4; H, 2·4. $C_{14}H_8ON_2F_6$ requires C, 50·3; H, 2·4%).

The azoxy-compound (0·50 g.), ethyl alcohol (5 c.c.) and Raney nickel (*ca.* 1 g.) were shaken together in hydrogen until absorption was complete. The solution was filtered, a little concentrated hydrochloric acid was added, and the alcohol was evaporated *in vacuo*. The residual salt was diazotised in the usual way and then β-naphthol (0·45 g.), in aqueous sodium hydroxide, was added. The precipitate, recrystallised from ethyl alcohol, gave **3**-trifluoromethylphenylazo-β-naphthol (0·56 g.), m. p. and mixed m. p. 165—166°.

4 : 4′-*Diamino*-2 : 2′-*bistrifluoromethyldiphenyl*.—**3** : 3′-Bistrifluoromethylazobenzene (5·00 g.), ethyl alcohol (75 c.c.), water (5·0 c.c.), and sodium amalgam (Na, 1·5 g.; Hg, 70 g.) were shaken together vigorously until the solution was colourless (*ca.* 5 min.), and then poured into 1 : 1 (vol.) sulphuric acid–water (200 c.c.) at 40—50°. A red precipitate was deposited, and after being recrystallised from aqueous alcohol this regenerated starting material (1·40 g.) had m. p. and mixed m. p. 79°. The aqueous layer was neutralised with sodium hydroxide (5N) and extracted with ether, and the extracts were washed, dried ($MgSO_4$), and evaporated, leaving a semi-solid residue. After the addition of a little light petroleum (b. p. 40—60°) the solution (A) was filtered and the solid was recrystallised from aqueous ethyl alcohol, to give **4** : 4′-diamino-2 : 2′-bistrifluoromethyldiphenyl (0·55 g.), m. p. 180—182°, not depressed in admixture with the product described by Pettit and Tatlow (*loc. cit.*) (Found : C, 52·4; H, 3·1. Calc. for $C_{14}H_{10}N_2F_6$: C, 52·5; H, 3·1%). Treatment, in ether, with excess of trifluoroacetic anhydride (Bourne, Henry, Tatlow, and Tatlow, *J.*, 1952, 4014) gave the *bistrifluoroacetyl* derivative (84%) m. p. 209—210° (Found : C, 42·4; H, 1·7. $C_{18}H_8O_2N_2F_{12}$ requires C, 42·2; H, 1·6%). The sulphate of this benzidine, and that of the **3** : 3′-bistrifluoromethyl isomer, are fairly soluble in water.

Concentration of the solution (A) gave a mixture of oil (1·87 g.) and crystals; the crystals were separated, washed with light petroleum (b. p. 40—60°), and recrystallised from ethyl alcohol. The *product* (0·078 g.) had m. p. 141°, depressed in admixture with the above benzidine derivative (Found : C, 52·4; H, 3·4. $C_{14}H_{10}N_2F_6$ requires C, 52·5; H, 3·1%).

2 : 2′-*Bistrifluoromethyldiphenyl*.—**4** : 4′-Diamino-2 : 2′-bistrifluoromethyldiphenyl (2·50 g.) was tetrazotised, using sodium nitrite (1·2 g.), concentrated hydrochloric acid (4·0 c.c.), and water (20 c.c.). Hypophosphorous acid (16 c.c., 30%) was added, and after 1 hr. at 0° and 2 hr. at 15° the mixture was distilled in steam, the distillate was ether-extracted, the extracts were dried ($MgSO_4$) and evaporated, and the residue was distilled, to give **2 : 2′-*bistrifluoromethyldiphenyl*** (1·34 g.), b. p. 230°, m. p. 32° [after nucleation with a solid specimen prepared by an Ullmann reaction on *o*-iodobenzotrifluoride (Pettit and Tatlow, unpublished results)] (Found : C, 58·2; H, 2·8. $C_{14}H_8F_6$ requires C, 57·9; H, 2·8%).

2 : 2′-Bistrifluoromethyldiphenyl (0·204 g.) was stirred mechanically with concentrated sulphuric acid (2·0 c.c.) at 90° for ½ hr. and at 100° for 3 hr. The mixture was poured into ice-water, the aqueous phase was extracted with ether, and the ethereal extracts were washed with aqueous alkali. The ethereal phase retained a neutral substance (0·06 g.), later shown to be 4-trifluoromethylfluorenone (Pettit and Tatlow, unpublished). The alkaline washings were acidified (H_2SO_4) and extracted with fresh ether, and these ethereal layers were washed, dried ($MgSO_4$), and evaporated, to give, after recrystallisation from ethyl alcohol, 9-oxofluorene-4-carboxylic acid (0·050 g.), m. p. and mixed m. p. 226—227° (Found : C, 74·8; H, 3·6. Calc. for $C_{14}H_8O_3$: C, 75·0; H, 3·6%). Graebe and Aubin (*loc. cit.*) gave m. p. 227°.

2 : 2′-*Bistrifluoromethylazobenzene*.—*o*-Nitrobenzotrifluoride (Jones, *J. Amer. Chem. Soc.*, 1947, **69**, 2346), (6·50 g.) was reduced electrolytically (5 amp.) as described for the *m*-isomer, a smaller apparatus being used. The solid product, recrystallised from aqueous ethyl alcohol, afforded red **2 : 2′-*bistrifluoromethylazobenzene*** (1·41 g.), m. p. 126—128° (Found : C, 52·6; H, 2·5; F, 35·4. $C_{14}H_8N_2F_6$ requires C, 52·8; H, 2·5; F, 35·8%).

2 : 2′-*Bistrifluoromethylhydrazobenzene*.—(a) *Preparation.* The **2** : 2′-bistrifluoromethylazo-compound (1·0 g.), ethyl alcohol (30 c.c.), water (2·0 c.c.), and sodium amalgam (Na, 1·0 g.; Hg, 50 g.) were shaken together until the red colour was discharged (*ca.* 2 min.); then the solution was poured into concentrated hydrochloric acid (50 c.c.) containing ice (50 g.). The precipitate, recrystallised from aqueous alcohol, afforded colourless **2 : 2′-*bistrifluoromethyl-***

hydrazobenzene (0·90 g.), m. p. 122—123° (depressed in admixture with the starting material) (Found: C, 52·5; H, 3·0; F, 35·3. $C_{14}H_{10}N_2F_6$ requires C, 52·5; H, 3·1; F, 35·6%).

The hydrazo-compound (0·50 g.) was hydrogenated and the product was coupled as described for 3 : 3′-bistrifluoromethylazoxybenzene, to give, after recrystallisation from ethyl alcohol, red *2-trifluoromethylphenylazo-β-naphthol* (0·58 g.), m. p. 157—158°, alone and in admixture with the product prepared directly from *o*-aminobenzotrifluoride (Pettit, Stacey, and Tatlow, unpublished) (Found: C, 64·5; H, 3·2; F, 17·9. $C_{17}H_{11}ON_2F_3$ requires C, 64·5; H, 3·5; F, 18·0%).

The hydrazo-compound was insoluble in cold aqueous acids, and it could not be diazotised and coupled with β-naphthol.

(b) *Benzidine transformation.* The 2 : 2′-hydrazo-compound (0·42 g.) was heated with sulphuric acid (8 c.c.) and water (4 c.c.) at 90° for 2 hr. with stirring. The reddish insoluble material, recrystallised from aqueous alcohol, gave 2 : 2′-bistrifluoromethylazobenzene (0·01 g.), m. p. and mixed m. p. 125°. The acid solution was neutralised with aqueous sodium hydroxide; extraction with ether followed by drying ($MgSO_4$) and evaporation of the extracts afforded a solid, which, after three recrystallisations from aqueous alcohol, gave 4 : 4′-diamino-3 : 3′-bistrifluoromethyldiphenyl (0·15 g.), m. p. and mixed m. p. 115° (Found: C, 52·2; H, 3·0. Calc. for $C_{14}H_8N_2F_6$: C, 52·5; H, 3·1%). Treatment of the product, in ether, with excess of trifluoroacetic anhydride, followed by evaporation *in vacuo* with several portions of carbon tetrachloride, afforded the bistrifluoroacetyl derivative, m. p. (unchanged by recrystallisation) and mixed m. p. 201°. Pettit and Tatlow (*loc. cit.*) gave m. p. s 115—116·5° and 202° respectively.

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407. *Nitramines and Nitramides. Part IV.* The Acid-catalysed Decomposition of Primary Nitramines.*

By J. BARROTT, I. N. DENTON, and ALEX. H. LAMBERTON.

The decomposition of primary nitramines by aqueous acids probably proceeds by formation of nitramine ($NH_2{\cdot}NO_2$) and an alkyl cation. The former then yields nitrous oxide and water, whilst the latter reacts with water to give an alcohol, or loses a proton to yield an olefin, or combines with anions (*e.g.*, Cl^-) which are present in the solution. The reaction is bimolecular, the rate being $\propto [H^+][R{\cdot}NH{\cdot}NO_2]$, and is formulated as an S_E2 substitution on the "amino"-nitrogen atom: $R{\cdot}NH{\cdot}NO_2 + H^+ \longrightarrow R^+ + NH_2{\cdot}NO_2$. Electron-donation by R seems to favour decomposition, though $Bu^t{\cdot}NH{\cdot}NO_2$ is anomalous; relative rates are: R = Pr^i > Et or Bu^t > Me ≫ $CH_2{\cdot}CO_2H$. Precise results could not be obtained for the step-wise decomposition of the common dinitramines, but the rates fall qualitatively into a similar order.

THE decomposition of primary nitramines by aqueous sulphuric acid was investigated by early workers (Van Romburgh, *Rec. Trav. chim.*, 1888, **7**, 246; Franchimont and Klobbie, *ibid.*, p. 350; Van Erp, *ibid.*, 1895, **14**, 40; Franchimont and Umbgrove, *ibid.*, 1898, **17**, 287), who found that nitrous oxide was the main, and probably the only, nitrogenous product. The reaction was formulated as $R{\cdot}NH{\cdot}NO_2 \longrightarrow ROH + N_2O$; but this appears to be an over-simplification, since Van Erp (*loc. cit.*) found that *n*-hexylnitramine yielded (besides nitrous oxide) two hexyl alcohols, a hexene, and a dihexyl ether. Van Romburgh (*loc. cit.*) found that ethylenedinitramine gave rise to an aldehyde: this was shown to be acetaldehyde by Lamberton, Lindley, Owston, and Speakman (*J.*, 1949, 1645).

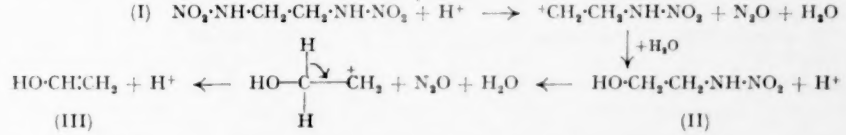
We have re-investigated briefly the products of decomposition. In preliminary experiments, accurate to 5%, it was found that methyl-, ethyl-, and *iso*propyl-nitramine yielded, respectively, 1·0, 1·2, and 1·15 mols. of gas when heated with 0·5M-sulphuric acid,

* Part III, *J.*, 1952, 1886.

whilst ethylenedinitramine yielded 1·95 mols. under the same conditions. Methylnitramine gave 1·45 mols. of gas on being heated with 1·0M-hydrochloric acid. In all cases 93—98% of the gas evolved could be removed by dissolution in ethanol: 98% of nitrous oxide was found in a more precise analysis of the gas evolved from methylnitramine and dilute sulphuric acid. Tomlinson (*J. Org. Chem.*, 1952, **17**, 648) appears to imply that a considerable quantity of nitrogen is produced from ethylenedinitramine and dilute sulphuric acid, but we are informed (personal communication) that this analysis is suspect, and under re-examination.

The excess of gas from ethyl- and *iso*propyl-nitramine was presumably (cf. Van Erp, *loc. cit.*) the corresponding olefin and, apart from a qualitative confirmation—by bubbling it through bromine water—was not specifically investigated. The unexpected excess of alcohol-soluble gas from methylnitramine and 1·0M-hydrochloric acid was shown to be methyl chloride by treatment of the alcoholic solution with pyridine and recognition of the ionisable chloride thus formed. Methyl chloride was not formed from methyl alcohol and hydrochloric acid under comparable conditions; this suggested, and subsequent experiments largely confirmed, that methyl ions were formed during the decomposition. The production of alkyl cations also affords a ready explanation of the formation of olefins, and of the conversion of ethylenedinitramine (I), *via* 2-hydroxyethylnitramine (II), into acetaldehyde (III).

The non-gaseous reaction products were also examined. Methylnitramine (0·05M) gave a 95% yield of methyl alcohol, as determined by chromic acid oxidation of the residual solution in 0·5M-sulphuric acid after complete decomposition, and the remainder of the original alkyl content may have been converted into methyl hydrogen sulphate, which is stable to the oxidising agent. Ethylenedinitramine under similar conditions gave a 46% yield of acetaldehyde, as determined by precipitation of the 2 : 4-dinitrophenylhydrazone; the results of chromic acid oxidation were consonant with the formation of *ca.* 45% of acetaldehyde and 55% of ethylene glycol. Trimethylenedinitramine (0·05M) in sulphuric acid (0·5M) gave, apparently, some propaldehyde; purification of the 2 : 4-dinitrophenylhydrazone was difficult and we submit this conclusion with reserve. No trace of 2 : 4-dinitrophenylhydrazones was obtained from any of the mononitramines.



Apart from Tomlinson's work (*loc. cit.*) on ethylenedinitramine, which came to our notice after the completion of the major part of this research, no kinetic investigation of the decomposition has been published. The course of the reaction has been followed by measurement of the increase in pressure of gas confined at constant volume and temperature over a solution of the nitramine in dilute sulphuric acid; and, when the content of mineral acid was not more than four times that of the nitramine, by direct titration with alkali. In the first of these methods it is assumed that the measured rate of gas evolution, of whatever nature, is proportional to the rate of decomposition of the primary nitramine. We believe this assumption to be justified since (1) the formation of an olefin from an alkyl cation must be relatively very rapid, and (2) we have shown that nitramine ($NH_2 \cdot NO_2$), which we consider to be an intermediate, decomposed (in the conditions employed) at least ten times faster than any of the primary nitramines investigated. Furthermore, the second (acidimetric) method gave, in the cases where it could be employed, results in reasonable agreement with those obtained manometrically. These conclusions apply to the mononitramines but not, without qualification (p. 2001), to the step-wise decomposition of dinitramines such as (I).

At constant acidity the mononitramines were found, by either method, to decompose in good accordance with the first-order reaction-rate law. The first-order rate coefficients thus obtained were directly proportional to the hydrogen-ion content of the solutions.

The reaction is thus bimolecular, and its speed proportional to $[H^+][R{\cdot}NH{\cdot}NO_2]$. Table 1 gives in column 5 the measured first-order coefficients, and in column 6 the corresponding second-order coefficients. Though the results obtained by acidimetry were of the same order

TABLE 1. *Decomposition of the nitramines,* $R{\cdot}NH{\cdot}NO_2$, *initially* 0·05M *in aqueous sulphuric acid, at* 85° ± 0·2°.

1	2	3	4	5	6
Run no.	R	H_2SO_4 (mole/l., at 20°)	Method employed	First-order rate coefficient, 10^3k (min.$^{-1}$)	Second-order rate coefficient, 10^3k [(mole/l.)$^{-1}$ min.$^{-1}$]
I, II	Me	0·500	Manometric	14·8, 15·7	31
XXVIII	,,	0·050	Acidimetric	1·5	30
III, IV	Et	0·500	Manometric	18·1, 18·3	37
V	,,	0·250	,,	9·9	41
VI	,,	0·050	,,	1·9	38
XXIX, XXX	,,	0·050	Acidimetric	2·5, 2·5	50
VII, VIII	Pr^i	0·500	Manometric	26·8, 25·6	54
IX	,,	0·250	,,	14·0	57
X	,,	0·100	,,	5·5	56
XI	,,	0·050	,,	2·7	54
XXXI to XXXVI	,,	0·050	Acidimetric	2·7 to 3·4	63
XLIV	Bu^t	0·101	Acidimetric	4·1	41
XLV, XLVI	,,	0·050	,,	2·0, 2·0	40
XII	$CH_2{\cdot}CO_2H$	0·500	Manometric	0·6	1

Values in column 6 are the average of the figures in column 5, divided by the appropriate value of $[H^+]$.

as those obtained manometrically, they tended to be higher, especially in the case of ethylnitramine. The manometric results were more consistent than the acidimetric, but we believe the latter to be a sounder measure, in theory, of the rate of decomposition. It would be over-confident to assert that the true rates of decomposition have been ascertained with a precision greater than, say, 20%; but it can be seen that the second-order rate coefficient at 85° [10^3k, (mole/l.)$^{-1}$ min.$^{-1}$] is about 30 for methylnitramine, 40 for ethyl- or *tert.*-butyl-nitramine, 60 for *iso*propylnitramine, and only 1 for nitramino-acetic acid.

We suggest that the rate-determining stage of the decomposition should be formulated as $R{\cdot}NH{\cdot}NO_2 + H^+ \longrightarrow R^+ + NH_2{\cdot}NO_2$, that is, as an S_E2 substitution of R by H on the "amino"-nitrogen atom. It would be possible to formulate the reaction as proton addition, followed by ionisation of $[R{\cdot}N_2H_2O_2]^+$: on grounds of simplicity we prefer the single-stage reaction. The nitramine ($NH_2{\cdot}NO_2$) formed subsequently yields nitrous oxide and water, whilst the alkyl cation attacks, in the main, water to yield the alcohol ROH and restore the hydrogen-ion concentration of the solution.

Two points, at least, arise from this hypothesis. First, if a primary nitramine is decomposed by heating it with water alone, the reaction should no longer be pseudo-unimolecular, since the hydrogen-ion concentration falls as the nitramine is destroyed. In theory, since primary nitramines are weak acids, $[H^+] \propto \sqrt{[\text{Nitramine}]}$, and the order of reaction should be 1·5. To obtain measurable rates of reaction, we were obliged to work with concentrated (up to 2M) solutions of methylnitramine and, even so, only the first 20% of decomposition could be observed in a reasonable time. The order of the reaction was about 1·3 with respect to the methylnitramine, and the rate was clearly dependent upon the initial concentration. Similar results (see p. 2004) have been obtained by the use of ethylenedinitramine.

Secondly, the formation of alkyl cations should be capable of quantitative as well as qualitative demonstration. If the alkyl ions react with chloride ions instead of water, the overall decomposition becomes $R{\cdot}NH{\cdot}NO_2 + H^+ + Cl^- \longrightarrow RCl + H_2O + N_2O$. The acidity of the solution decreases by two equivalents for every equivalent of the primary nitramine destroyed, and one equivalent of chloride ion disappears. This effect has been demonstrated in certain cases. A 1·0M-solution of the nitramine in 1·02M-hydrochloric acid was kept at 85° until decomposition was complete, and the percentage yield of alkyl

halide determined by (*a*) the reduction in Cl^- content and (*b*) the fall in acidity over and above that due to the disappearance of the primary nitramine. As expected, the yields indicated (see Table 2) were reduced in less concentrated hydrochloric acid, and enhanced by the addition of chloride ions in the form of sodium chloride.

Since *iso*propylnitramine yielded (Table 2) so little alkyl halide even in 1·0M-hydrochloric acid, rate determinations of the usual (acidimetric) kind could be made in more dilute hydrochloric acid. These (Table 3) showed that the rate was the same as that in sulphuric acid yielding the same concentration of hydrogen ions, and was unaffected by the addition of sodium chloride.

TABLE 2. *Production of alkyl chlorides from nitramines in aqueous hydrochloric acid, at 85° ± 0·2°.*

Nitramine	HCl (mole/l., at 20°)	Yield % of R·Cl by determn. of: H^+	Cl^-
1·0M-$Me{\cdot}NH{\cdot}NO_2$	1·02	50	48
0·5M- ,,	0·52	37	35
0·25M- ,,	0·52	39, 40	39, 37
0·25M- ,,	0·51 (+ 0·5M-NaCl)	67	67
1·0M-$Et{\cdot}NH{\cdot}NO_2$	1·02	14	14
1·0M-$Pr^i{\cdot}NH{\cdot}NO_2$	1·02	2	2

The decomposition of the first three members of the dinitramine series has been investigated briefly by the manometric method. Gas evolution at constant acidity no longer took place in accordance with the first-order law, and the apparent rate of reaction increased during the decomposition. This is the result to be expected from successive decompositions of comparable speed. 2-Hydroxyethylnitramine (II), the probable initial product from ethylenedinitramine, can be prepared (at least in a crude form) and was found to decompose, in 0·5M-sulphuric acid, at 85°, at the first-order rate $10^3k = 11{\cdot}5$ min.$^{-1}$. The complete curve of gas evolution from ethylenedinitramine was consonant with this value for the second stage, and $10^3k = 7{\cdot}5$ min.$^{-1}$ in 0·5M-sulphuric acid, at 85°, for the initial conversion into 2-hydroxyethylnitramine.

Tomlinson (*loc. cit.*) has measured the rate of decomposition of ethylenedinitramine by cooling samples and weighing the residual nitramine which separated. His value (k = 0·175 hr.$^{-1}$ in 0·48M-sulphuric acid, at 84°, using logarithms to base 10), when converted into our units and corrected for a slight difference in acidity ($10^3k = 7{\cdot}0$ min.$^{-1}$ in 0·5M-sulphuric acid, at 84°) is close to our quite independent estimate. Using Tomlinson's method, we have recently examined the decomposition of ethylenedinitramine in water at 98°. Our values, though not in close agreement, were of the same magnitude as his. We found,

TABLE 3. *Decomposition of* iso*propylnitramine, initially* 0·05M *in aqueous hydrochloric acid, at 85° ± 0·2°.*

1	2	3	4
Run no.	HCl (mole/l., at 20°)	First-order coefficient, 10^3k (min.$^{-1}$)	Second-order coefficient, 10^3k [(mole/l.)$^{-1}$ min.$^{-1}$]
XXXIX, XL	0·204	12·1, 12·5	62
XXXVII, XXXVIII	0·102	5·9, 5·8	59
XLI	0·052	2·9	57
XLII	0·052 (+0·05M-NaCl)	2·9	57
XLIII	0·052 (+ 0·5M-NaCl)	3·3	65

Measurements were made by the acidimetric method. Values in column 4 are the average of the figures in column 3, divided by the appropriate value of $[H^+]$.

as expected, that the rate of decomposition was dependent upon the initial concentration of ethylenedinitramine.

The second-order rate coefficients for the initial stage of the decomposition of methylene-, ethylene-, and trimethylene-dinitramine could be estimated, very roughly, as $10^3k = 7$, 15, and 30, respectively [(mole/l.)$^{-1}$ min.$^{-1}$]. These estimates, taken with the values found for the mononitramines (Table 1), suggest that electron-donation by R favours, and electron attraction by R hinders, the acid-catalysed decomposition of $R{\cdot}NH{\cdot}NO_2$.

tert.-Butylnitramine is an exception to this generalisation. It may be relevant to note that an S_E2 substitution on an atom attached to a *tert.*-butyl group might have steric features in common with an S_N2 substitution of a *neo*pentyl halide.

Experimental

Reaction rates were evaluated on the basis of natural logarithms and are given in units of 10^3k. The hydrogen-ion concentration at 85° has been calculated on the assumption, valid to the degree of accuracy employed, that the solutions showed the same expansion as water between 20° and 85°, *i.e.*, that the concentration of acid (mole/l. at 85°) was 97% of that determined, and tabulated, for the solvents at 20°. Account has been taken, by extrapolation from Hamer's results (*J. Amer. Chem. Soc.*, 1934, **56**, 860), of the second stage of ionisation of sulphuric acid. For example, dilute sulphuric acids of 0·500, 0·250, 0·100, and 0·050 molarity at 20° have been calculated to be, respectively, 0·486, 0·244, 0·098, and 0·050M in hydrogen ions at 85°.

Materials.—The known nitramines were prepared by standard methods. Methylnitramine was finally purified by sublimation at 15 mm. on to a " cold-finger " (bath at 70°). Ethyl- and *iso*propyl-nitramine were distilled at, respectively, 98°/15 mm. and 95—96°/17 mm. The purity of the samples used was checked by titration with standard alkali.

tert.-*Butylnitramine.*—*N-tert.*-Butylnitrourethane (22·8 g.) (Curry and Mason, *J. Amer. Chem. Soc.*, 1951, **73**, 5043) and *iso*propylamine (14·2 g.) were mixed, in dry ether, and set aside overnight. The feathery needles of the *iso*propylamine salt (15 g.) were collected and acidified with potassium dihydrogen phosphate (29 g. in 210 ml. of water), and the free nitramine was extracted with ether. Evaporation and distillation yielded solid tert.-*butylnitramine* (8·2 g.) (b. p. 94—95°/16 mm.; 71°/0·6 mm.); prisms of m. p. 38° were obtained by dissolution in ether, addition of *n*-hexane, and slow evaporation at room temperature (Found: C, 39·8; H, 8·4%; equiv., 118. $C_4H_{10}O_2N_2$ requires C, 40·7; H, 8·5%; equiv., 118).

2-Hydroxyethylnitramine was obtained as an oil (Franchimont and Lublin, *Rec. Trav. chim.*, 1902, **21**, 50) of equiv. 112 (calc. for $C_2H_6O_3N_2$: 106).

Analysis of the Gas evolved on Decomposition.—The nitramine (*ca.* 1 mmole of a mono-, or 0·5 mmole of a di-nitramine) was weighed into a small tube and placed in a 200-ml. flask fitted with a 10-cm. condenser and a sealed-in tap-funnel whose stem extended nearly to the bottom of the flask. The shaft of a mercury-sealed stirrer passed through the condenser, and a side arm, above the level of the condenser jacket, was connected to a delivery tube passing into 40% aqueous potassium hydroxide. The apparatus was first flushed, through the tap-funnel, with carbon dioxide from a cylinder. The stream of carbon dioxide was then cut off, and the tap-funnel filled with the appropriate solvent (*e.g.*, 20 ml. of 0·5M-H_2SO_4). After flushing out of the small residual space in the funnel, a slower stream of gas, from powdered carbon dioxide, was introduced into the apparatus simultaneously with the opening of the tap. Residual traces of air passed up a column of the aqueous potassium hydroxide and were sucked over into, and expelled from the cup of, an attached (mercury-filled) Lunge nitrometer. Decomposition of the nitramine was then brought about by heating it on a water-bath. The gas evolved was absorbed by successive (5 ml.) portions of ethanol, the saturated ethanol being expelled from the cup of the nitrometer, and the residual gas stored meanwhile over the aqueous potassium hydroxide. Blank tests showed that a small correction (0·5 ml.) was required. The results are given in Table 4.

Table 4. *Mols. of gas (corrected values) from various nitramines.*

Compound	Solvent	Total gas (mols.)	Residual gas (insol. in EtOH) (mols.)
$Me{\cdot}NH{\cdot}NO_2$	1·0M-HCl	1·51, 1·43	0·06, 0·05
,, ...	0·5M-H_2SO_4	0·98, 0·98	0·04, 0·07
$Et{\cdot}NH{\cdot}NO_2$	,,	1·20	0·07
$Pr^i{\cdot}NH{\cdot}NO_2$	,,	1·16	0·06
$(CH_2{\cdot}NH{\cdot}NO_2)_2$	,,	1·97, 1·96	0·13, 0·04

To obtained a more precise result a sample of gas (from methylnitramine and sulphuric acid) was collected by the method described in Part II (*J.*, 1951, 1288), though, for convenience, a gas sampling tube was used in place of the bulb *E* (*loc. cit.*). The gas was washed with fuming sulphuric acid to remove methyl alcohol, and then with alkaline pyrogallol; nitrous oxide and nitrogen were determined by sparking with an excess of hydrogen, and measurement of the residual volume. Measurements were made over mercury, but in presence of sufficient water to effect saturation; blank corrections, evaluated by the use of pure nitrous oxide, were made to

allow for the dissolution of this gas in sulphuric acid and in alkaline pyrogallol. Values obtained, after the removal of methyl alcohol vapour, were O_2, 1%; N_2O, 98%; N_2, 1%.

Analysis of the Non-gaseous Products of Decomposition.—Quantitative oxidation with chromic acid was carried out by Blank and Finkelbeiner's method (*Ber.*, 1906, **39**, 1326; see also Beckurts, "Die Methoden der Massanalyse," Braunschweig, 1913, p. 398). It was assumed that ethylene glycol and acetaldehyde (from ethylenedinitramine) were converted into oxalic and acetic acid.

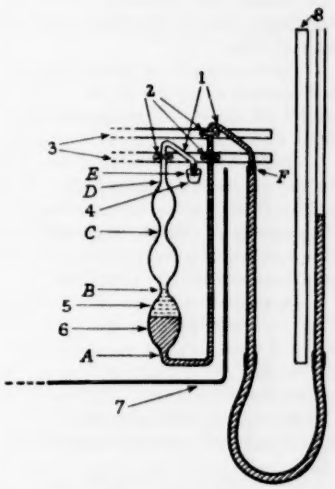
The pure 2 : 4-dinitrophenylhydrazone of acetaldehyde was obtained without difficulty. The solution obtained by the complete decomposition of trimethylenedinitramine in 0·5M-sulphuric acid yielded a crude 2 : 4-dinitrophenylhydrazone, m. p. 146—147° after repeated crystallisation from ethanol, undepressed by mixture with authentic propaldehyde 2 : 4-dinitrophenylhydrazone of m. p. 154° (Found: C, 45·1; H, 4·1. Calc. for $C_9H_{10}O_4N_4$: C, 45·4; H, 4·2%).

Measurement of Reaction Rates.—(a) *Manometric technique.* One of the two containers used is shown in the Figure. In operation the two similar containers were clamped permanently to the frame, and were lowered into, or raised from, the thermostat as a unit. One container held

1, *Capillary tubing*
2, *Clamps*
3, *Rigid frame*
4, *Half-bored rubber bung*
5, *Solution*
6, *Mercury*
7, *Thermostat wall*
8, *Fixed scale*

Volumes (ml.)		
Container	1	2
AB	19·61	19·30
BC	10·03	9·65
CD	8·38	7·33
DE	0·15	0·15

E *and* F *are bent forward, and lie outside the thermostat*



a solution of the nitramine, and the other, filled in a similar manner, the solvent only. The differences in pressure between the two containers were measured, and corrections for variations in (*a*) external pressure and temperature, and (*b*) the vapour pressure of the solvent, were thus unnecessary. A freshly prepared standard solution of the nitramine in dilute sulphuric acid was held, in a small flask, at *E*. A few drops of mercury were expelled from the capillary, and the reservoir was then lowered to draw a known volume (*CE*) of solution into the container. The supply was then removed from *E*, and the reservoir lowered to fill *CE* with air. The outside of the capillary was dried, and the outlet closed with a thick rubber cap (a rubber bung bored half-way through) containing a little mercury, some of which was forced up the capillary tube. The cap was sealed to the tube by "Picein" wax. In this way the solution and gas were confined between mercury "plugs," and any leak was shown by the escape of mercury. The container could be charged in less than 5 min. from the dissolution of the nitramine, and separate experiments showed that no observable decomposition occurred in 20 min. at room temperature. Owing to the low solubility of ethylenedinitramine it was necessary, in this case only, to charge the containers with solutions at 40°.

The containers were lowered into the glass-walled thermostat, and readings of pressure made with the aqueous level in each container at *B*. A flail attached to the stirrer agitated the container holding the nitramine solution.

The decomposition was completed by heating (generally overnight) for at least twice the period required for 90% decomposition, and the final difference in mercury levels (D_f) measured with care. The mercury level from the control container 2 was, owing to mechanical differences

such as the permanent position of clamping, slightly higher than that from container 1, even when both contained dilute sulphuric acid at 85°. This constant (C) was measured, and the value of ($D_t + C$) taken to indicate complete decomposition. If, at the time t, the difference in levels was D_t, then the indicated residual nitramine was $(D_f + C) - (D_t + C) = D_f - D_t$.

In operation there was an induction period (*ca.* 10—20 min.) greater than might be reasonably ascribed to thermal equilibration: if, however, the retained gas remained constant, then the slope of the lines obtained by plotting the logarithm of apparent residual concentration against time gave the true rate of reaction (cf. Marlies and La Mer, *J. Amer. Chem. Soc.*, 1935, **57**, 1812). The total quantity of gas evolved in this apparatus was always 10—15% less than that measured by the " sweep-through " technique.

(b) *Acidimetric technique.* Equal volumes (5 ml.) of standard solutions of (*a*) the nitramine in water and (*b*) the mineral acid were mixed to give a solution of the reported concentration. This was heated, under a ground-glass reflux condenser, in a 25-ml. flask immersed to the neck in the thermostat. After cooling, the whole content was titrated (thymolphthalein) to give one point on the decomposition curve. Prolonged heating led, as expected, to disappearance of the nitramine, but retention of the mineral-acid acidity. *tert.*-Butylnitramine was not sufficiently soluble to give a 0·1M-solution in water: portions were weighed individually into the flasks, and dissolved in 1 min. on swirling in the thermostat. Tests showed that the solutions reached thermal equilibrium 3 min. after insertion in the thermostat: this was taken as zero time.

Decomposition of Methylnitramine in Water.—Samples (5 ml.) were heated in sealed tubes for periods of up to 48 hr. at 98° ± 0·2°. A 15—20% reduction in acidity was observed by direct titration. The approximate first-order rate coefficients [10^3k (min.$^{-1}$) at 98°] were 0·08, 0·10, and 0·12, for methylnitramine solutions of, respectively, 0·5, 1·0, and 2·0 molarity at 20°.

Indirect Measurement of the Alkyl Halide Produced.—Solutions were prepared and heated as in the acidimetric technique. After a sufficient time they were cooled, titrated with alkali, acidified with a few drops of acetic acid, and re-titrated with silver nitrate (dichlorofluorescein). The results (Table 2), evaluated from the fall in Cl^- and the fall in acidity over and above that due to the disappearance of the nitramine, would not have been consistent unless decomposition had been essentially complete.

Investigation of the Dinitramines by the Manometric Technique.—Plotting the logarithm of the " residual percentage " (more correctly, the percentage of the total gas still to be evolved) against time did not yield straight lines. Various values were assumed for the first and second unimolecular decomposition coefficients, and the curves so obtained compared with the experimental values. Values in reasonable agreement with the experimental data are given in Table 5; they are probably of the right order but, particularly in the case of the second stage, should not be regarded as more than a rough approximation.

TABLE 5. *Probable rates of decomposition of dinitramines in* 0·5M-*sulphuric acid, at* 85° ± 0·2°.

Compound (initially 0·025M)	First stage of decomp., 10^3k_1 (min.$^{-1}$)	Second stage of decomp., 10^3k_2 (min.$^{-1}$)
$CH_2(NH{\cdot}NO_2)_2$	3·5	7
$(CH_2{\cdot}NH{\cdot}NO_2)_2$	7·5	11·5 *
$CH_2(CH_2{\cdot}NH{\cdot}NO_2)_2$	15	30

* Confirmed directly by use of 2-hydroxyethylnitramine.

Decomposition of Nitramine ($NH_2{\cdot}NO_2$).—The manometric technique was used, though the speed of decomposition was rather high for our apparatus. The unimolecular character of the decomposition led, as expected, to similar reaction rates (10^3k = 330 ± 30 min.$^{-1}$) in 0·5 and in 0·05M-sulphuric acid at 85°. This is more than ten times as fast as the decomposition of any of the primary nitramines investigated; and though the production of $NH_2{\cdot}NO_2$ as an intermediate may lead to a slight delay in the initial production of gas, it cannot have a significant effect upon the slope of the lines obtained by plotting the logarithm of (apparent) residual concentration against time.

Decomposition of Ethylenedinitramine in Water.—We have used, essentially, Tomlinson's method (*loc. cit.*). Solutions were made up, on a w/w basis, by heating and stirring under reflux in the thermostat. Samples (*ca.* 10 ml.) were withdrawn by means of a pre-heated untipped pipette, cooled, and weighed. The precipitated ethylenedinitramine was collected in a sintered-glass crucible, and the mother-liquor titrated with alkali. We found that the titration values increased (from *ca.* 2 to *ca.* 6 ml. of 0·2N-NaOH) during the decomposition.

This was presumably due to the accumulation of water-soluble 2-hydroxyethylnitramine in the system; we have thought it best to employ a uniform correction factor (at least for each concentration of ethylenedinitramine) to allow for the slight solubility of the dinitramine in water. These factors, based on sampling as soon (15—20 min.) as dissolution and thermal equilibration was complete, were 25, 30, 39, and 36 mg. of ethylenedinitramine from 10-g. samples of 2·97, 5·79, 10·74, and 10·88% (w/w) concentration. Standardised conditions of precipitation, filtration, and washing were used: the variations in the correction factor were probably due to the variations in the bulk of material available for dissolution in the washing process. By heating for 48 hr. at 97—98° from 20 to 40% (according to concentration) of the material was decomposed. For solutions containing 2·97, 5·79, 10·74, and 10·88% (w/w) of ethylenedinitramine (*ca.* 0·19, 0·39, 0·72, and 0·73M at 97° by measurement of density to two places of decimals), we found apparent unimolecular " constants " [10^3k (min.$^{-1}$)] of, respectively, 0·07 at 97°, 0·08 at 97°, 0·16 at 97·6°, and 0·17 at 97·2°. Tomlinson reported, in our units, 0·077 for 0·784M-ethylenedinitramine in water at 98°. Though the reaction is probably of fractional order with respect to the dinitramine, little sign of this can be expected to appear in the first 30% of decomposition from any one initial concentration.

We thank Mr. V. C. Broom for the precise gas analysis.

THE UNIVERSITY, SHEFFIELD, 10. [*Received, February 20th,* 1953.]

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408. *The Reaction of Amino-compounds with Sugars. Part II.* The Action of Ammonia on Glucose, Maltose, and Lactose.*

By L. HOUGH, J. K. N. JONES, and E. L. RICHARDS.

D-Psicose has been isolated from the products formed by reaction of D-glucose with aqueous ammonia at 37°. Lactose and maltose in aqueous ammonia are isomerised to lactulose and maltulose respectively. Alkaline degradation of lactose takes place with the production of D-galactose and its isomerisation products, while maltose produces D-glucose and its isomerisation products.

LOBRY DE BRUYN and VAN EKENSTEIN (*Rec. Trav. chim.*, 1895, **14**, 195) reported that weak alkali causes isomerisation of reducing sugars at room temperature, glucose, for example, being transformed *via* the 1 : 2-enediol to a mixture of glucose, mannose, and fructose. In addition, a second ketose, *pseudo*fructose, which is probably formed *via* the 2 : 3-enediol, was obtained in an impure state (*idem, ibid.*, 1897, **16**, 257, 274); subsequent authors have named this sugar D-psicose and D-allulose. The identity of Lobry de Bruyn's product with D-psicose has been in doubt because of their observation that *pseudo*fructose is fermentable by yeast, whereas synthetic D-psicose is not (Steiger and Reichstein, *Helv. Chim. Acta*, 1936, **19**, 184). Other workers (de Whalley, Albon, and Gross, *Analyst*, 1951, **76**, 287; Schneider and Erlemann, *Zucker-Beihefte*, 1951, **3**, 41) have confirmed this formation of a second ketohexose, which Zerban, Sattler, Rosenthal, and Glaubach (*Sugar*, 1952, **47**, [2], 33) isolated and characterised as D-psicosazone. D-Psicose has been found in very small amounts in distillery slop (Zerban and Sattler, *Ind. Eng. Chem.*, 1942, **34**, 1180) where it may be an artefact formed by the lime used in sugar manufacture. Zerban, Sattler, Rosenthal, and Glaubach (*loc. cit.*) recently showed that D-psicose is formed even when a solution of D-fructose is heated. In Part I, the complex mixture resulting from the reaction of D-glucose with aqueous ammonia at 37° was described as containing a ketohexose which was indistinguishable from psicose on paper chromatograms. This identification was confirmed by the preparation of the crystalline phenylosazone which was identical with D-psicosazone, and of crystalline 1 : 2-3 : 4-di*iso*propylidene D-psicofuranose, which had properties identical with those described by Steiger and Reichstein (*loc. cit.*). It was observed that D-psicose was not fermented by yeast.

Either lactose or maltose with aqueous ammonia develops a reddish-brown colour.

* Part I, *J.*, 1952, 3854.

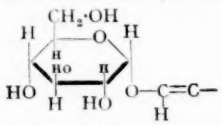
By following the course of the reactions on paper chromatograms it was observed that the disaccharides (aldobioses) were rapidly isomerised to glycosylketoses and that simultaneous alkaline fission took place, galactose and glucose (and their epimerisation products) being formed in good yield from lactose and maltose respectively.

The glycosylketose formed from lactose was isolated as a syrup and converted into the crystalline osazone which was identified as lactosazone. On hydrolysis the glycosylketose yielded D-galactose, characterised as the methylphenylhydrazone, and D-fructose characterised as the 2 : 3-4 : 5-di*iso*propylidene derivative. It is thus lactulose [4-(β-D-galactosyl)-D-fructose] which was prepared previously by the action of lime water on lactose (Montgomery and Hudson, *J. Amer. Chem. Soc.*, 1930, **52**, 2101).

Crystalline D-galactose was isolated from the lactose ammonia mixture and further characterised as the methylphenylhydrazone (cf. Lobry de Bruyn and van Ekenstein, *Rec. Trav. chim.*, 1899, **18**, 147; Corbett, Kenner, and Richards, *Chem. and Ind.*, 1953, 154); glucose was not detected. This mixture also contained a sugar which is tentatively identified as lyxose by paper chromatography; it has the same optical rotation as D-lyxose. However, as the sugar could be neither crystallised nor converted into a crystalline derivative, this identification as D-lyxose requires confirmation. The glycosylketose formed by isomerisation of maltose was isolated as the crystalline monohydrate. It gave maltosazone and, on hydrolysis, gave D-glucose, characterised as its osazone, and D-fructose characterised as described above. It is thus maltulose [4-(α-D-glucopyranosyl)-D-fructose]. Maltulose has been obtained as a syrup by the action of salivary α-amylase on the glycogen from livers of pregnant does and by the action of lime water on maltose (Peat, Roberts, and Whelan, *Biochem. J.*, 1952, **51**, xvii). Our product was indistinguishable on paper chromatograms from a specimen kindly supplied by Professor Peat, and has the same optical rotation. In addition to maltulose, the reaction of ammonia with maltose led to the formation of another glycosylketose which after hydrolysis gave spots on paper chromatograms corresponding to D-glucose, and to a ketohexose which was indistinguishable from psicose, but distinct from fructose, sorbose, and tagatose. This glycosylketose is thus very probably 4-(α-D-glucopyranosyl)-D-psicose, formed from maltose as psicose is formed from glucose.

D-Glucose from the alkaline fission of maltose was isolated and characterised as were mannose and fructose, and from paper chromatograms it appears that arabinose also is present. Lobry de Bruyn and van Ekenstein (*loc. cit.*, 1899), Kolb (*Biochem. Z.*, 1914, **63**, 1), and Evans and Benoy (*J. Amer. Chem. Soc.*, 1930, **52**, 294) have previously described the isolation of D-mannose phenylhydrazone from the products produced by the alkaline degradation of a solution of maltose.

These observations suggest that in the presence of ammonia an aldobiose is first isomerised to a glycosylketose and that the disaccharide is then degraded, perhaps to a compound of the type (I), which on hydrolysis would afford a reducing hexose, namely, glucose from maltose and galactose from lactose (cf. Isbell, *J. Res. Nat. Bur. Stand.*, 1941,



(I)

26, 35). As well as epimerisation, isomerisation, and fission products, strongly fluorescent materials were present in the products of the reaction of ammonia with lactose or maltose. These, in some cases, gave bright red colours when held over ammonia after being sprayed with diazotised sulphanilic acid, suggesting the presence of glyoxaline derivatives (see Part I).

Experimental

Analyses are by Mr. B. S. Noyes of Bristol. Evaporations were carried out under reduced pressure. The following solvent mixtures were used to separate the sugars by chromatography on Whatman No. 1 paper: (*a*) ethyl acetate–acetic acid–formic acid–water (18 : 3 : 1 : 4), (*b*) butanol–pyridine–water (10 : 3 : 3), and (*c*) butanol–ethanol–water (40 : 11 : 19).

Isolation of D-*Psicose* (D-*Allulose*).—Glucose (100 g.) was dissolved in water (1·6 l.) and ammonia (400 ml.; *d* 0·88). The solution was kept in a stoppered vessel (2 l.) at 37° for 48 hr. It was then concentrated to a syrup which was shaken with bromine water until a sample showed the absence of aldoses. Bromine was then removed from the solution by aeration, and lead acetate solution added dropwise until there was no further precipitation. The solution was then filtered, and dilute sulphuric acid added to the filtrate until no further precipitate was produced. The solution was again filtered and the filtrate freed from ions by treatment with Amberlite resins IR-120 and IR-4B. The neutral solution was concentrated to a syrup (*ca.* 25 g.), and a portion (7 g.) was transferred to a cellulose column and fractionated (cf. Hough, Jones, and Richards, *J.*, 1952, 3854). Concentration of the fraction of eluate which contained sugar with the characteristics of psicose gave a syrup A (0·2 g.), $[\alpha]_D^{20}$ +2° ± 1° (*c*, 1·9 in H_2O). On paper chromatograms, it showed the same colour reactions as a ketohexose and moved at the same rate as psicose, its position being charateristic since the other three ketohexoses moved more slowly (solvent *c*; see Part I). A solution of the sugar (0·17 g.) in water (4 ml.), phenylhydrazine (0·5 ml.), glacial acetic acid (0·6 ml.), and saturated sodium hydrogen sulphite solution (0·5 ml.) was heated on the boiling-water bath for 30 min. On cooling, yellow crystals (0·14 g.) separated. After two recrystallisations from aqueous ethanol, and a third from benzene they had m. p. 166°, undepressed on admixture with an authentic specimen of D-psicosazone (m. p. 166°) (Found: C, 60·2; H, 6·25; N, 15·2. Calc. for $C_{18}H_{22}O_4N_4$: C, 60·4; H, 6·15; N, 15·6%). When recrystallised from aqueous ethanol, they showed $[\alpha]_D^{19}$ −30° [*c*, 0·52 in EtOH (2·5 ml.) and pyridine (0·1 ml.)] ⟶ −20° ± 3° (equilm., 24 hr.). Steiger and Reichstein (*Helv. Chim. Acta*, 1936, **19**, 184) record $[\alpha]_D^{20}$ −19·2° ± 4° (*c*, 1·0 in absolute EtOH), and Zerban and Sattler (*Ind. Eng. Chem.*, 1942, **34**, 1184) give $[\alpha]_D^{25}$ −41·8° [in EtOH (1·5 pts.) and pyridine (1 pt.)] ⟶ −22·1° (equilm., 24 hr.). On recrystallisation from benzene, different values were obtained, *viz.*, $[\alpha]_{17}^{D}$ −19° [*c*, 0·96 in EtOH (1·5 ml.) and pyridine (1 ml.)] ⟶ −45° (equilm., 24 hr.). D-Psicose was obtained in lower yield when the bromine oxidation was omitted.

1 : 2-3 : 4-*Diiso*propylidene D-*Psicofuranose*.—A second sample of the syrup A (0·3 g.) was dissolved in methanol containing glass balls, then evaporated, and the residue was warmed under reduced pressure for 3 hr., to give a dry syrup. Dry acetone (10 ml.), anhydrous copper sulphate (0·1 g.), and concentrated sulphuric acid (0·03 g.) were then added. The mixture was shaken for 4 days and set aside for a further 3 days. The 1 : 2-3 : 4-di*iso*propylidene compound was then isolated as described by Bell (*J.*, 1947, 1461) for 2 : 3-4 : 5-di*iso*propylidene fructose. The syrup obtained crystallised at *ca.* −40°, and recrystallised from light petroleum (b. p. 40—60°) as plates, m. p. 57—58°, $[\alpha]_D^{18}$ −93° (*c*, 0·23 in $COMe_2$). (Found: C, 55·4; H, 7·7. Calc. for $C_{12}H_{20}O_6$: C, 55·3; H, 7·7%). Steiger and Reichstein (*Helv. Chim. Acta*, 1936, **19**, 184) record m. p. 57—58·5° and $[\alpha]_D^{20}$ −98·2° (*c*, 2·124 in $COMe_2$).

Fermentation of Reaction Mixture.—Glucose, fructose, and mannose were removed from a portion of the brown reaction mixture, from which ammonia had been removed by evaporation under reduced pressure, by fermentation with baker's yeast. The residual unfermentable ketohexose was isolated by separation on sheets of filter paper (solvent *c*) as described earlier (Hough, Jones, and Richards, *loc. cit.*). The syrup, $[\alpha]_D^{22}$ 0° ± 2° (*c*, 1·0 in H_2O), moved at the same rate and gave the same colour reactions as psicose on paper chromatograms and yielded a phenylosazone, m. p. 163°, with a crystalline form indistinguishable from that of psicosazone.

Reaction of Lactose with Ammonia.—Lactose (10 g.) was dissolved in water (200 ml.) and ammonia (50 ml.; *d* 0·88). The solution was kept in a stoppered vessel (250 ml.) at 37° for 2 days in the absence of air (rigorous exclusion of air was however not attempted), gradually becoming brown. Paper chromatographic examination showed it to be an exceedingly complex mixture. Evaporation of the reaction mixture left a brown syrup (9·2 g.) which was transferred to a column of cellulose and fractionated by partition chromatography. The effluent was collected portionwise and after examination on paper chromatograms, grouped into six fractions, which were concentrated.

Fraction 1. This (0·32 g.) consisted of materials which trailed on paper chromatograms, were strongly fluorescent, and gave red colours with ammonia after being sprayed with diazotised sulphanilic acid, suggesting the presence of glyoxalines.

Fraction 2. This (0·2 g.), a light brown syrup, gave two spots on a paper chromatogram (solvent *c*). It was separated on sheets of filter paper (solvent *c*) as described by Hough, Jones, and Richards (*loc. cit.*), into two fractions. Fraction A (0·12 g.) consisted of materials giving a pink colour with *p*-anisidine hydrochloride spray, and also after being sprayed with diazotised sulphanilic acid a red colour with ammonia. It was dissolved in water (5 ml.) and shaken

with Amberlite resins IR-120 and IR-4B until the solution no longer gave a reaction with the diazotised sulphanilic acid spray, indicating the absence of glyoxalines. It was concentrated to a syrup (0·075 g.) which gave the colour reactions characteristic of a pentose and moved to the same position as xylose and/or lyxose (solvent *c*). In phenol–water, it behaved as lyxose, but differently from xylose (cf. Hough and Jones, *J.*, 1951, 1122). The syrup {$[\alpha]_D^{15}$ −13° (*c*, 1·3 in H_2O)} did not crystallise. Fraction B (0·045 g.) was a syrup which on paper chromatograms, moved to the same position as, and gave colour reactions characteristic of, tagatose.

Fraction 3. This material (1·5 g.) crystallised as the solvent was removed. On paper chromatograms (solvents *a*, *b*, and *c*) it was indistinguishable from D-galactose; it had m. p. 163°, $[\alpha]_D^{20}$ +105° (*c*, 1·0 in H_2O) ⟶ +80° (equilm., 24 hr.); the methylphenylhydrazone had m. p. and mixed m. p. 189° (Found: N, 10·2. Calc. for $C_{13}H_{26}O_5N_2$: N, 9·9%).

Fraction 4. This, a syrup (1·2 g.), $[\alpha]_D^{19}$ −12° (*c*, 0·69 in H_2O), gave the red colour with the resorcinol–hydrochloric acid spray characteristic of a ketohexose. A solution of the sugar (0·063 g.) in methanol (10·5 ml.) containing hydrogen chloride (0·03 g.) showed $[\alpha]_D^{19}$ +15° (¾ hr.) ⟶ +18° (2 hr.) ⟶ +9° (4 hr.) ⟶ +2·5° (2 days). The sugar, when heated with aqueous phenylhydrazine acetate, gave lactosazone, m. p. and mixed m. p. 204°, the sugar being thus identified as lactulose.

Hydrolysis of lactulose: The sugar (0·14 g.) was hydrolysed with 2% oxalic acid at 100° overnight. The acid was removed by shaking the solution with Amberlite resin IR-4B, and the solution filtered and concentrated. Paper chromatographic analyses of the concentrate indicated the presence of galactose and fructose, which were separated on sheets of paper (cf. Hough, Jones, and Richards, *loc. cit.*). The ketose fraction (0·04 g.) was converted into 2 : 3-4 : 5-di*iso*propylidene fructose (by Bell's method, *J.*, 1947, 1461), m. p. and mixed m. p. 93°, $[\alpha]_D^{20}$ −22° ± 6° [*c*, 0·94 in H_2O (0·5 ml.)]. The aldose fraction gave D-galactose methylphenylhydrazone, m. p. 185°, mixed m. p. 187°.

Fraction 5. This (2·3 g.) was largely unchanged lactose which gave a phenylosazone, m. p. and mixed m. p. 204°.

Fraction 6. After the lactose had been removed completely, the column was eluted with ethanol and then with water, and the combined eluates were evaporated to a brittle brown glass (1·1 g.). This did not move on paper chromatograms (solvent *c*) and in solution gave a bluish green fluorescence.

Reaction of Maltose with Ammonia.—Maltose (10 g.), dissolved in water (200 ml.) and ammonia (50 ml.; *d*, 0·88), was kept in a stoppered vessel (250 ml.) at 37° for 3 days during which it gradually developed a reddish-brown colour. Paper chromatographic examination showed it to be an exceedingly complex mixture. The reaction mixture was concentrated to a syrup which was fractionated as described above.

Fraction 1. This (0·82 g.) was found on paper chromatograms to consist of at least three components of R_G 0·68, 0·57, and 0·47—0·27 (solvent *c*), which moved more slowly than tetramethyl glucose (R_G 1). The compound with R_G 0·68, after being sprayed with diazotised sulphanilic acid, gave a bright red colour with ammonia, and a brown spot with the ammoniacal silver nitrate spray, and was weakly fluorescent. The material of R_G 0·57 behaved similarly except that it was strongly fluorescent. The materials which moved at rates between R_G 0·47 and 0·27 gave a bright red band with a yellow centre at R_G 0·40 when held over ammonia after being sprayed with diazotised sulphanilic acid and with ammoniacal silver nitrate spray gave a brown band with a white centre at R_G 0·40. The band was also weakly fluorescent.

Fraction 2. This (0·9 g.) showed on paper chromatograms a trace of a material giving the colour reactions of a pentose and moving to the same position as arabinose. The fraction consisted mainly of D-fructose and D-mannose. D-Fructose was characterised as its 2 : 3-4 : 5-di*iso*propylidene derivative, m. p. and mixed m. p. 92°, $[\alpha]_D^{20}$ −32° (*c*, 0·74 in H_2O). Mannose was characterised as the insoluble mannose phenylhydrazone, m. p. 193°.

Fraction 3. This (1·1 g.) showed the presence of glucose only, on paper chromatograms. The syrup crystallised from methanol–butanol, and then had m. p. 146—147°, $[\alpha]_D^{18}$ +92° (*c*, 1·66 in H_2O) ⟶ +50° (equilm., 24 hr.). It gave glucosazone, m. p. 201°; and a glucosotriazole, m. p. 193—194°, $[\alpha]_D^{18}$ −81° [*c*, 0·67 in pyridine (cf. Hann and Hudson, *J. Amer. Chem. Soc.*, 1944, **66**, 735)].

Fraction 4. This (0·5 g.) contained maltose, and a glycosylketose moving at a rate similar to that of maltose on paper chromatograms; this was identified as maltulose. In order to isolate a quantity of the sugar and identify it, the conditions of preparation were slightly modified. The mixture described above was kept for only 24 hr. and then concentrated. The solution was shaken with bromine in the presence of an excess of barium benzoate for 3 days.

The ketoses were then isolated as described for psicose. *Maltulose monohydrate* (R_g 0·074) (3·17 g.) crystallised from dioxan–methanol when the solvent was allowed to evaporate slowly at room temperature (Found: C, 40·1; H, 6·7. $C_{12}H_{22}O_{11},H_2O$ requires C, 40·0; H, 6·7%), and had m. p. 113—115° (decomp.), $[\alpha]_D^{20}$ +58° (*c*, 1·58 in H_2O) ⟶ +64° (equilm.). When it was heated with phenylhydrazine acetate solution, maltosazone (m. p. and mixed m. p. 202°) was produced in characteristic crystalline form.

Hydrolysis of Maltulose.—The sugar was hydrolysed with 0·1N-sulphuric acid at 100° overnight. The solution was neutralised by shaking it with Amberlite resin IR-4B, filtered, and concentrated to a syrup, chromatographic analysis of which (solvents *a*, *b*, and *c*) indicated the presence of glucose and fructose. These were separated on sheets of filter paper (solvent *c*). The glucose was characterised as the phenylosazone, m. p. and mixed m. p. 205°, identical with D-glucosazone, and fructose as its 2 : 3-4 : 5-di*iso*propylidene derivative, m. p. and mixed m. p. 93°, $[\alpha]_D^{19}$ −32° (*c*, 0·62 in H_2O).

We thank Professor S. Peat, F.R.S., for the gift of a specimen of maltulose. One of us (E. L. R.) thanks the New Zealand Defence Science authorities for an award.

THE UNIVERSITY, BRISTOL. [*Received, March 17th*, 1953.]

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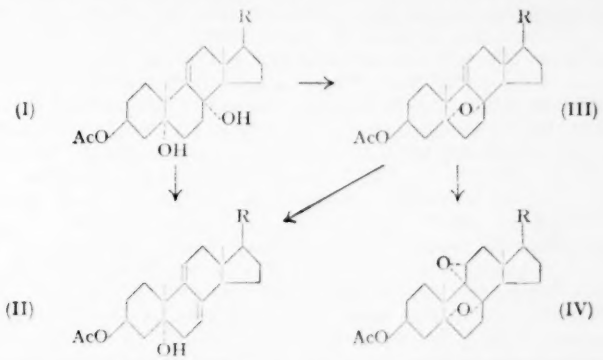
409. *Studies in the Steroid Group. Part LIX.* Preparation and Reactions of 5α : 8α-Epoxy-Δ⁹⁽¹¹⁾-steroids.*

By R. B. CLAYTON, A. CRAWSHAW, H. B. HENBEST, E. R. H. JONES, (MISS) B. J. LOVELL, and GEOFFREY W. WOOD.

5α : 8α-Dihydroxy-Δ⁹⁽¹¹⁾-steroids, prepared by reduction of 9(11)-dehydroergosterol epidioxide, are converted by acetic acid into 5α : 8α-epoxy-Δ⁹⁽¹¹⁾-compounds. Some reactions of this new class of steroid epoxides are described.

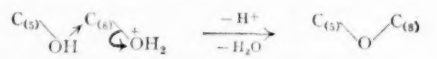
ONE of the aims in preparing 5α : 8α-dihydroxy-Δ⁹⁽¹¹⁾-steroids (I) (by reduction of dehydroergosterol epidioxide; cf. Part LVI, *J.*, 1952, 4883) was to find out whether rearrangements of the allylic 8-hydroxy-Δ⁹⁽¹¹⁾-system to give 11-substituted Δ⁸⁽⁹⁾ compounds could be effected (cf. the rearrangement of 5-hydroxy-Δ⁶- to 7-halogeno-Δ⁵-steroids, Henbest and Jones, *J.*, 1948, 1792). In the present instances, such rearrangements have not been accomplished because under most isomerisation conditions these 5 : 8-dihydroxy-Δ⁹⁽¹¹⁾-compounds were dehydrated to 7 : 9-dienes (II). This dehydration could be carried out quantitatively with dilute mineral acids (Part LVI).



Treatment of these 5 : 8-diols with organic acids, such as acetic acid, also resulted in the loss of the elements of water, but the products obtained (in good yield) were 5α : 8α-epoxides (III). The new compounds were characterised, first, by their relative ease of

* Part LVIII, *J.*, 1952, 4894.

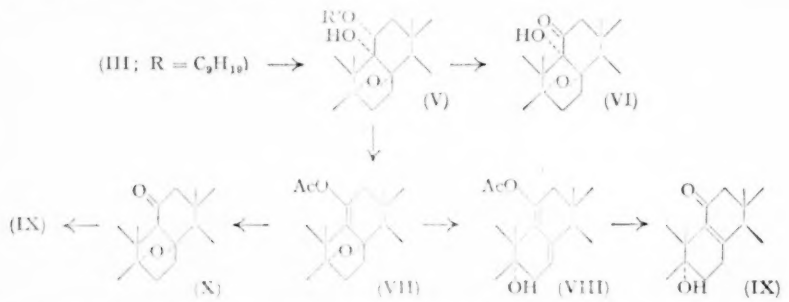
elution from alumina, their lack of characteristic absorption in the ultra-violet above 2200 Å, and the ease with which they were converted by traces of mineral acid into the isomeric 5-hydroxy-7 : 9-dienes (II). The formation of these epoxides parallels the formation of 1 : 4-cineole from 1 : 4-dihydroxy-*p*-menthane (cf. Wallach, *Annalen*, 1912, **392**, 62), and mechanistically may be represented thus:



The configuration of the epoxide bridge must be α in view of the formation from 5α : 8α-diols. Models show that ring B is most likely to adopt a boat conformation in compounds with the stereochemistry of these 5 : 8-diols. In this conformation, the 5α- and the 8α-hydroxyl group are close to each other, and thus favourably disposed for intramolecular dehydration (the formation of these epoxides is discussed further in the following paper).

The reactivity towards oxidising agents of the 9 : 11-ethylenic bond in these 5 : 8-epoxy-compounds was much greater than in the corresponding steroids with a 5 : 8-epidioxy-linking (cf. Part LVIII, *J.*, 1952, 4894). For instance, (III; R = C_9H_{19}), with potassium permanganate in acetic acid or with organic peracids, afforded good yields of the diepoxide (IV; R = C_9H_{19}), whereas the reaction between the 5 : 8-epidioxy-compounds and organic peracids was very slow, and permanganate largely attacked the 12-position. With limited amounts of these oxidising agents and the $\Delta^{9:22}$-5 : 8-epoxide (III; R = C_9H_{17}), some preferential oxidation of the $\Delta^{9(11)}$-bond took place and moderate yields of (IV; R = C_9H_{17}) could be obtained. Permanganate oxidation of (III; R = C_9H_{17}) resulted also in partial degradation of the side chain, yielding the diepoxy-acid (IV; R = CHMe·CO_2H), and in some preferential attack at the Δ^{22}-bond, for methyl 3β-acetoxy-5α-hydroxybisnorchola-7 : 9-dienate could be isolated after treatment of the reaction product with dilute mineral acid and then diazomethane, indicating the presence in the total product of (III; R = CHMe·CO_2H).

Perhaps the greatest difference in reactivity of the $\Delta^{9(11)}$-bond in the 5 : 8-epoxy- and -epidioxy-compounds was towards osmium tetroxide, for whereas the latter class did not react, the former, exemplified by (III; R = C_9H_{19}), gave an addition complex and thence the 9α : 11α-diol (V; R′ = H), the configuration being indicated by the ready formation of an 11-acetate (V; R′ = Ac). Chromic acid oxidised the 9 : 11-diol to the ketol (VI), but attempts to replace the 9-hydroxyl group by hydrogen *via* halogeno-compounds by the methods used by Heymann and Fieser (*J. Amer. Chem. Soc.*, 1951, **73**, 5254) for a similar ketol lacking the oxide bridge were unsuccessful; the 9-hydroxyl group was very unreactive, probably for steric reasons.

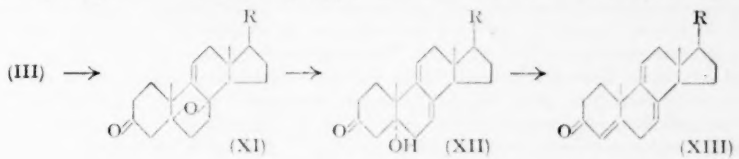


Attempted dehydration of the diol (V; R′ = H) with thionyl chloride in pyridine gave the 9 : 11-sulphite ester, but treatment of the 11-acetoxy-9-hydroxy-compound (V; R′ = Ac) with thionyl chloride in pyridine resulted in ready *trans*-elimination of the elements of water (with ring B necessarily in the boat and ring C in the chair form the 9α-hydroxyl group and the 11β-hydrogen atom are both polar and coplanar with $C_{(9)}$ and

$C_{(11)}$), with the formation of the enol acetate (VII). This was readily isomerised by dilute mineral acid to the 5-hydroxy-7 : 9-diene (VIII) ($\lambda_{max.}$ 2450 Å), although this was not obtained crystalline. Dilute alkaline hydrolysis of the doubly unsaturated enol acetate (VIII) or the epoxy-enol acetate (VII) gave a solution with $\lambda_{max.}$ 2540 Å, corresponding to an 11-keto-$\Delta^{8(9)}$-structure (IX), the intensity of absorption indicating the presence of about 70% of the conjugated ketone. The preparation by other routes of compounds with structure (IX) will be dealt with in a separate paper. The formation of such a conjugated ketone from (VII) on treatment with alkali clearly proceeds *via* the epoxy-ketone (X); the isomerisation of this to (IX) is analogous to the rearrangement of 7-keto-9α : 11α-epoxides to 11α-hydroxy-7-keto-$\Delta^{8(9)}$-steroids (cf. Stork, Romo, Rosenkranz, and Djerassi, *ibid.*, p. 3546).

Reduction of the 5 : 8-oxide system was also studied in view of the possibility of preparing 5-hydroxy-$\Delta^{9(11)}$-compounds. No reaction took place with lithium aluminium hydride until the temperature was raised to the b. p. of dibutyl ether; a mixture was then obtained (some diene, probably 7 : 9, was detected spectroscopically) in which the 5-hydroxy-$\Delta^{8(9)}$ (and possibly the -Δ^{7})-compound was probably present, for treatment with hydrogen–platinum–acetic acid gave 3β-acetoxyergost-8(14)-en-5α-ol. Catalytic hydrogenation was likewise difficult to achieve but using a relatively large amount of Adams catalyst in acetic acid caused uptake of one mol., 3β-acetoxyergost-8(14)-en-5α-ol being isolated; this was probably formed from the 5-hydroxy-7 : 9-diene produced by isomerisation of the epoxide.

Oppenauer oxidation of 3-hydroxy-5 : 8-epoxides yielded ketones (XI), which were fairly stable towards alkali, in contrast to the 7-keto-9 : 11-epoxides and 11-keto-5 : 8-epoxide discussed above. As expected, these ketones were readily isomerised to 7 : 9-dienes (XII) with traces of mineral acid. Dehydration of (XII) was best effected with the weak alkaline reagent, aluminium *tert.*-butoxide, which afforded, when R = C_9H_{17}, the same ketone (XIII) as was obtained by Oppenauer oxidation of 9 : 11-dehydroergosterol.



Experimental

In this and the following paper m. p.s were determined on a Kofler block and are corrected. Optical rotations were determined with chloroform solutions in a 1-dm. semi-micro tube at room temperature (18—25°). P. Spence (Grade H) alumina was used for chromatography; " deactivated alumina " signifies that it had been treated with 5% or 10% acetic acid as described by Farrar, Hamlet, Henbest, and Jones (*J.*, 1952, 2657).

3β-*Acetoxy*-5α : 8α-*epoxyergosta*-9 : 22-*diene* (III; R = C_9H_{17}).—A solution of 3β-acetoxyergosta-9 : 22-diene-5α : 8α-diol (8 g.) in acetone (180 c.c.) and acetic acid (10 c.c.) was heated under reflux for 1 hr. The solvents were then removed under reduced pressure and the residue was introduced in benzene on to a column of alumina (200 g.). Elution with benzene (600 c.c.) gave the 5 : 8-*epoxide* (6 g.), crystallising from methanol as needles, m. p. 115—117°, $[\alpha]_D$ +31° (*c*, 1·15) (Found : C, 79·4; H, 10·3. $C_{30}H_{46}O_3$ requires C, 79·25; H, 10·2%). Elution with ether–methanol (3 : 1) afforded, after crystallisation from acetone, 3β-acetoxyergosta-7 : 9 : 22-triene-5α-ol (1·6 g.) as large plates, m. p. 213—216°, $[\alpha]_D$ +48° (*c*, 0·84).

Hydrolysis (5% methanolic potassium hydroxide) of the epoxy-acetate afforded 5α : 8α-*epoxyergosta*-9 : 22-*dien*-3β-*ol*, crystallising from methanol as laths, m. p. 131—132°, $[\alpha]_D$ +26° (*c*, 0·84) (Found : C, 81·65; H, 10·7. $C_{28}H_{44}O_2$ requires C, 81·5; H, 10·75%).

3β-*Acetoxy*-5α : 8α-*epoxyergost*-9-*ene* (III; R = C_9H_{19}).—This was prepared (in similar yield) as described for the Δ^{22}-compound. The acetate crystallised from methanol as blunt needles, m. p. 106—108°, $[\alpha]_D$ +62° (*c*, 1·2) (Found : C, 78·9; H, 10·9. $C_{30}H_{48}O_3$ requires C, 78·85; H, 10·6%). Alkaline hydrolysis gave 5α : 8α-*epoxyergost*-9-*en*-3β-*ol*, m. p. 102—106°, $[\alpha]_D$ +55° (*c*, 0·95) (after crystallisation from methanol) (Found : C, 81·1; H, 11·25. $C_{28}H_{46}O_2$ requires C, 81·1; H, 11·2%).

Acidic Isomerisation of 5α : 8α-*Epoxy*-$\Delta^{9(11)}$-*steroids.*—(*a*) 5α : 8α-Epoxyergost-9-en-3β-ol (70 mg.) was dissolved in hot methanol and a trace of concentrated hydrochloric acid was added. After 3 min. a dense precipitate of glistening plates was produced. After cooling to 20°, the precipitated ergosta-7 : 9-diene-3β : 5α-diol (60 mg.; m. p. 211—220°) was recrystallised from acetone, giving a product with m. p. and mixed m. p. with an authentic sample 214—220°, $[\alpha]_D$ +44° (*c*, 1·0). Light absorption : Max. 2420 A; ε = 17,000.

(*b*) 3β-Acetoxy-5α : 8α-epoxyergost-9-ene (150 mg.) in hot methanol (3 c.c.) was treated with a trace of concentrated hydrochloric acid. A precipitate separated almost immediately. Cooling the mixture gave 3β-acetoxyergosta-7 : 9-dien-5α-ol (120 mg.), m. p. 195—202°. Recrystallisation from acetone gave material (100 mg.) of m. p. and mixed m. p. with an authentic sample 209—213°, $[\alpha]_D$ +60° (*c*, 1·0). Light absorption : Max. 2420 Å; ε = 17,300.

3β-*Acetoxy*-5α : 8α-9α : 11α-*diepoxyergostane* (IV; R = C_9H_{19}).—(*a*) 3β-Acetoxy-5α : 8α-epoxyergost-9-ene (1 g.) in dry chloroform (2 c.c.) was treated with chloroform (15 c.c.) containing 2·5 mols. of perbenzoic acid. The solution was kept at 20° for 3 days, whereafter the steroid was isolated with chloroform in the usual way. One crystallisation from methanol gave a product (0·78 g.), m. p. 145—150°; a second crystallisation from methanol afforded the *diepoxide* with m. p. 146—150·5°, $[\alpha]_D$ +52° (*c*, 0·93) (Found : C, 76·0; H, 10·1. $C_{30}H_{48}O_4$ requires C, 76·2; H, 10·25%). Absence of appreciable absorption at 2050—2200 and 2900 Å indicated the absence of olefinic and carbonyl groups (absence of the latter was confirmed by the infra-red spectrum).

(*b*) A solution of potassium permanganate (130 mg.) in the minimum amount of acetic acid–water (1 : 1) was added to 3β-acetoxy-5α : 8α-epoxyergost-9-ene (300 mg.) in acetic acid (10 c.c.). The mixture was kept at 20° for 90 min., the steroid being then isolated with ether. Crystallisation from methanol gave the diepoxide (170 mg.), m. p. and mixed m. p. 147—149·5°, $[\alpha]_D$ +54° (*c*, 0·92).

(*c*) A mixture of 3β-acetoxy-5α : 8α-epoxyergost-9-ene (350 mg.) in dioxan (7·5 c.c.) and chloroform (5 c.c.), formic acid (1·5 c.c.), and 100-vol. hydrogen peroxide (1·5 c.c.) was kept at 20° for 60 hr. Isolation with ether and crystallisation from methanol afforded the diepoxide, m. p. 143—144·5°, $[\alpha]_D$ +58° (*c*, 1·0).

3β-*Acetoxy*-5α : 8α-9α : 11α-*diepoxyergost*-22-*ene* (IV; R = C_9H_{17}).—A solution of permonophthalic acid (1 mol.) in ether (25 c.c.) was added to a solution of 3β-acetoxy-5α : 8α-epoxyergosta-9 : 22-diene (3 g.) in ether (25 c.c.). The mixture was kept at 0° for 24 hr. and then at 25° for 48 hr., then diluted with ether and washed successively with sodium carbonate and ferrous sulphate solutions, dried (Na_2SO_4), and evaporated. Concentrated hydrochloric acid (4 drops) was added to a solution of this product in hot methanol. The solution was allowed to cool to 25° and the steroid was isolated with ether. The resulting product in benzene was introduced on to alumina (300 g.). Elution with benzene (600 c.c.) afforded the *diepoxide* (940 mg.) which crystallised from methanol as large needles, m. p. 157·5—159°, $[\alpha]_D$ +21° (*c*, 1·72) (Found : C, 76·5; H, 9·85. $C_{30}H_{46}O_4$ requires C, 76·6; H, 9·9%). Elution with ether–methanol (3 : 1) gave, after recrystallisation from acetone, 3β-acetoxyergosta-7 : 9 : 22-trien-5α-ol, m. p. 214—217°, $[\alpha]_D$ +50° (*c*, 0·83).

Alkaline hydrolysis of this diepoxide yielded 5α : 8α-9α : 11α-*diepoxyergost*-22-*en*-3β-*ol*, crystallising from methanol as plates, m. p. 186—188°, $[\alpha]_D$ +14° (*c*, 1·03) (Found : C, 78·3; H, 10·35. $C_{28}H_{44}O_3$ requires C, 78·45; H, 10·35%).

Reaction of 3β-*Acetoxy*-5α : 8α-*epoxyergosta*-9 : 22-*diene with Potassium Permanganate.*—(*a*) Potassium permanganate (490 mg.) in acetic acid (12 c.c.) and water (2 c.c.) was added dropwise to a solution of the epoxy-diene (600 mg.) in acetic acid (8 c.c.) during 5 min. After being kept at 20° for 1 hr. the mixture was poured into water, and the steroid isolated with ether. The ethereal solution was washed with 2% potassium hydroxide solution (see below), dried, and evaporated. The residue (470 mg.) after seven recrystallisations from methanol afforded almost pure 3β-acetoxy-5α : 8α-9α : 11α-diepoxyergost-22-ene (80 mg.) as needles, m. p. 151—153·5°, $[\alpha]_D$ +24°; mixed m. p. with an authentic sample (see above) 152—158°. Acidification of the alkali extract gave (by ether-extraction) some gummy acid (80 mg.), which was treated with diazomethane and then with 1 drop of hydrochloric acid in methanol, to yield methyl 3β-acetoxy-5α-hydroxybisnorchola-7 : 9-dienoate as plates, m. p. and mixed m. p. (cf. Part LVII, *J.*, 1952, 4890) 189—196°, $[\alpha]_D$ +73° (*c*, 0·53) (Found : C, 71·85; H, 9·05. Calc. for $C_{25}H_{36}O_5$: C, 72·1; H, 8·7%).

(*b*) Potassium permanganate (12 g.) in water (100 c.c.) and acetic acid (400 c.c.) was added with gentle swirling to the epoxy-diene (15 g.) in acetic acid (200 c.c.), with water cooling, and the solution was then kept at 20° for 40 min. The steroid was isolated with ether, the ethereal

solution then being extracted with 10% sodium carbonate solution. Acidification and ether-extraction afforded a crystalline acid (5 g.). Recrystallisation of a small amount of this from dioxan–*iso*propyl ether (1 : 1) gave 3β-*acetoxy*-5α : 8α-9α : 11α-*diepoxybisnorcholanic acid* as needles, m. p. 231—237°, $[\alpha]_D$ +42° (*c*, 1·27) (Found : C, 69·05; H, 8·0. $C_{24}H_{34}O_6$ requires C, 68·85; H, 8·2%). Excess of diazomethane in dry ether was added to part of the crude acid (1·35 g.). Removal of the ether gave a solid, which was dissolved in hot methanol, treated with 10 drops of hydrochloric acid, kept for 4 min., and then poured into water and ether. The ethereal extract yielded a solid which was chromatographed on deactivated alumina (150 g.). Elution with benzene (2 l.) gave *methyl* 3β-*acetoxy*-5α : 8α-9α : 11α-*diepoxybisnorcholanate* (770 mg.), long needles (from aqueous methanol), m. p. 158—159·5°, $[\alpha]_D$ +57° (*c*, 1·23). A portion was sublimed *in vacuo* for analysis (Found : C, 69·25; H, 8·35. $C_{25}H_{36}O_6$ requires C, 69·4; H, 8·4%). Further elution with benzene–ether (19 : 1) (2 l.) gave, after crystallisation from methanol, methyl 3β-acetoxy-5α-hydroxybisnorchola-7 : 9-dienoate (600 mg.) as plates, m. p. and mixed m. p. with an authentic sample 189—194°.

3β-*Acetoxy*-5α : 8α-*epoxyergostane*-9α : 11α-*diol* (V; R′ = H).—Solutions of 3β-acetoxy-5α : 8α-epoxyergost-9-ene (1·6 g.) in dry ether (15 c.c.) and of osmium tetroxide (1 g.) in dry ether were mixed, and pyridine (30 drops) was added. After 4 days at 20° the (now reddish-brown) solution was shaken overnight with an aqueous solution (200 c.c.) containing mannitol (20 g.) and potassium hydroxide (2 g.). The colourless ethereal layer was washed, dried, and evaporated, to give a pale brown solid (1·6 g.). This was chromatographed on alumina (100 g.), the fraction (1·1 g.) eluted with benzene–ether (1 : 1) being crystallised from methanol, to give the 9α : 11α-*diol* as fine needles, m. p. 192·5—194°, $[\alpha]_D$ +68° (*c*, 0·63) (Found : C, 73·5; H, 10·15. $C_{30}H_{50}O_5$ requires C, 73·45; H, 10·25%).

Attempted dehydration of this diol (110 mg.) with thionyl chloride (0·2 c.c.) in pyridine (3 c.c.) at 20° for 45 min., the steroid being isolated with ether, gave after two crystallisations from methanol the *sulphite* of the 9 : 11-diol as fine needles, m. p. 173—174°, $[\alpha]_D$ −28° (*c*, 0·37) (Found : C, 66·95; H, 9·0; S, 5·6. $C_{30}H_{48}O_6S$ requires C, 67·15; H, 9·2; S, 5·95%). Infra-red spectrum (in Nujol) : peaks at 1720 and 1245 (acetate) and 1215 cm.$^{-1}$ (sulphite; cf. Adams, Shafer, and Braun, *J. Amer. Chem. Soc.*, 1952, **74**, 5612).

3β : 11α-*Diacetoxy*-5α : 8α-*epoxyergostan*-9α-*ol* (V; R′ = Ac) *and* 3β : 11α-*Diacetoxy*-5α : 8α-*epoxyergost*-9-*ene* (VII).—A solution of the above 9 : 11-diol (150 mg.) in acetic anhydride (1·5 c.c.) and pyridine (3 c.c.) was heated at 100° for 8 hr. The product was isolated with ether; crystallisation from methanol yielded the 3 : 11-*diacetate*, m. p. 200—200·5°, $[\alpha]_D$ +64° (*c*, 0·71) (Found : C, 71·85; H, 9·85. $C_{32}H_{52}O_6$ requires C, 72·15; H, 9·85%).

Thionyl chloride (0·7 c.c.) was added to a solution of the diacetate (540 mg.) in pyridine (8 c.c.), and the mixture was then kept at 20° for 30 min. The steroid was isolated with ether and purified by chromatography on deactivated alumina (45 g.), elution with light petroleum–benzene (1 : 1) (600 c.c.) giving a solid (290 mg.), which on crystallisation from aqueous methanol afforded 3β : 11α-*diacetoxy*-5α : 8α-*epoxyergost*-9-*ene* as small needles, m. p. 149—152°, $[\alpha]_D$ +100° (*c*, 0·61) (Found : C, 74·95; H, 9·9. $C_{32}H_{50}O_5$ requires C, 74·65; H, 9·8%). Infra-red spectrum (in CCl_4) : peaks at 1750 and 1218 (enol acetate), 1730 and 1240 (3-acetate).

A solution of the enol-acetate (40 mg.) in methanol (15 c.c.) containing 15 drops of concentrated hydrochloric acid was kept at 20°. After 7 hr. the intensity at the absorption maximum (2450 Å) had become stationary (11,600), indicating the presence of about 70% of 7 : 9-diene (VIII). This compound was not obtained solid, but treatment of the product with 5% potassium hydroxide in methanol gave a solution with $\lambda_{max.}$ 2550 Å (ε = 7600). Similar alkaline treatment of 3β : 11α-diacetoxy-5α : 8α-epoxyergost-9-ene afforded a solution with $\lambda_{max.}$ 2530 Å (ε = 7200), the absorption in both cases corresponding to the presence of a 5α-hydroxy-11-keto-$\Delta^{8(9)}$-steroid (IX).

3β-*Acetoxy*-5α : 8α-*epoxy*-9α-*hydroxyergostan*-11-*one* (VI).—3β-Acetoxy-5α : 8α-epoxyergostane-9α : 11α-diol (110 mg.) in acetic acid (10 c.c.) was treated dropwise at 20° during 30 min. with chromic acid (30 mg.) in 70% acetic acid (3 c.c.), the mixture then being kept at 20° overnight. Excess of oxidising agent was reduced with methanol (2 c.c.), and the steroid isolated with ether. Crystallisation from methanol gave a good yield of the 11-*ketone* (VI), m. p. 204—206°, $[\alpha]_D$ +164° (*c*, 0·53) (Found : C, 73·8; H, 10·2. $C_{30}H_{48}O_5$ requires C, 73·75; H, 9·9%). Infra-red spectrum (in Nujol) : peaks at 3460 (hydroxyl), 1730 and 1250 (acetate), and 1695 cm.$^{-1}$ (11-ketone).

3β-*Acetoxyergost*-8(14)-*en*-5α-*ol from* (III; R = C_9H_{19}).—A solution of the epoxide (470 mg.) in acetic acid (20 c.c.) was shaken with Adams catalyst (150 mg.) and hydrogen. Uptake ceased when 1 mol. had been absorbed (1½ hr.). Filtration and removal of the solvent under

reduced pressure gave solid which yielded rods (220 mg.), m. p. 148—161°, from methanol. Further crystallisation afforded the pure $\Delta^{8(14)}$-compound, m. p. and mixed m. p. (sample prepared as described in Part LVI), 161—164°, $[\alpha]_D$ +3·5° (*c*, 1·1).

5α : 8α-*Epoxyergost*-9-*en*-3-*one* (XI; R = C_9H_{19}).—**5α : 8α**-Epoxyergost-9-en-3β-ol (750 mg.) was heated for 4 hr. under reflux with acetone (15 c.c.), and a 25% solution of aluminium *tert.*-butoxide in toluene (75 c.c.). The cooled mixture was stirred thoroughly with cold water, and the steroid was extracted with ether. Mesityl oxide was removed by evaporation with xylene under reduced pressure, and the product was chromatographed on deactivated alumina (70 g.). Elution with light petroleum–benzene (2 : 1) afforded a crystalline fraction (300 mg.), m. p. 163—168°, which gave the *ketone* as plates (from acetone), m. p. 165—167·5°, $[\alpha]_D$ +122° (*c*, 0·7) (Found: C, 81·8; H, 10·95. $C_{28}H_{44}O_2$ requires C, 81·5; H, 10·75%).

5α : 8α-*Epoxyergost*-9 : 22-*dien*-3-*one* (XI; R = C_9H_{17}).—This was prepared by Oppenauer oxidation of the 3β-sterol as described in the previous experiment. The *ketone* crystallised from methanol as needles, m. p. 147—150°, $[\alpha]_D$ +182° (*c*, 1·0) (Found: C, 81·9; H, 10·3. $C_{28}H_{42}O_2$ requires C, 81·9; H, 10·3%).

A yellow derivative was obtained on treating the ketone with 2 : 4-dinitrophenylhydrazine at 15°. It was filtered off rapidly and recrystallised twice from ethanol, to give small yellow needles melting over a wide range (190—215°), at the same time undergoing conversion into a dark red derivative. Light absorption of the yellow derivative (in chloroform): Max. 3700 Å; ε = 26,000 (cf. cholestanone 2 : 4-dinitrophenylhydrazone: Max. 3700 Å; ε = 24,500).

5α-*Hydroxyergosta*-7 : 9 : 22-*trien*-3-*one* (XII; R = C_9H_{17}).—The foregoing ketone (100 mg.), dissolved in ethanol (5 c.c.), was treated with a drop of concentrated hydrochloric acid, giving an immediate precipitate. Adddition of water gave more product; crystallisation of the total product from ethyl acetate gave the *hydroxy-ketone* as plates, m. p. 225—230°, $[\alpha]_D$ +76° (*c*, 0·5) (Found: C, 81·75; H, 10·25. $C_{28}H_{42}O_2$ requires C, 81·9; H, 10·3%). Light absorption: Max. 2440 Å; ε = 14,000.

This hydroxy-ketone (200 mg.) was dehydrated by a 25% solution of aluminium *tert.*-butoxide in toluene (20 c.c.) at 100° for 10 min. The product was isolated with ether and chromatographed on deactivated alumina (10 g.). Benzene–light petroleum (1 : 4) eluted a yellow gum (150 mg.) which crystallised in contact with acetone, giving a yellow solid, m. p. 110—130°. Several recrystallisations from aqueous acetone gave ergosta-4 : 7 : 9 : 22-tetraen-3-one (XIII) as plates, m. p. 141—145°, $[\alpha]_D$ +176° (*c*, 0·5), which on admixture with a sample, m. p. 140—145°, $[\alpha]_D$ +178°, prepared by Oppenauer oxidation of dehydroergosterol according to Heilbron, Kennedy, Spring, and Swain (*J.*, 1938, 869), gave no m. p. depression.

Dehydration of the hydroxy-ketone with sodium hydroxide or methoxide in methanol gave gums [owing to the instability of (XIII) towards strong alkali], and sublimation *in vacuo* afforded unchanged hydroxy-ketone.

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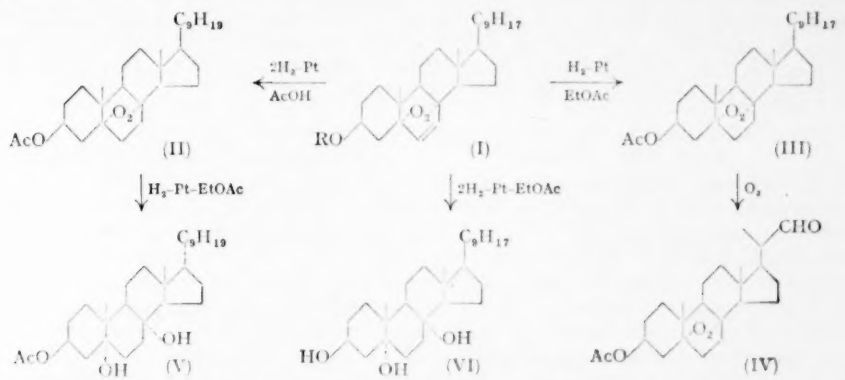
THE UNIVERSITY, MANCHESTER, 13. [*Received, February 27th*, 1953.]

410. *Studies in the Steroid Group. Part LX.* Reduction of Ergosterol Epidioxide.*

By R. B. Clayton, H. B. Henbest, and E. R. H. Jones.

As with dehydroergosterol epidioxide, hydrogenation of ergosterol epidioxide in the presence of platinum catalysts first leads to reduction of the Δ^6-bond. Further reduction takes place readily causing either saturation of the Δ^{22}-bond or fission of the epidioxide bridge (to furnish 5α : 8α-diols), depending on the experimental conditions. Dehydration of these 5α : 8α-diols yields 5α-hydroxy-Δ^7-compounds and 5α : 8α-epoxides; the properties of the latter are compared with those of the $\Delta^{9(11)}$-analogues described in the previous paper.

In Part LVI of this series (*J.*, 1952, 4883) the course of hydrogenation of 9 : 11-dehydroergosterol epidioxide under various conditions was reported. The present paper describes a comparative study of the reduction of ergosterol epidioxide. The only previous work on the hydrogenation of this compound was by Windaus, Bergmann, and Lüttringhaus (*Annalen*, 1929, **472**, 195) who described the formation of an "ergostenediol-I" when the epidioxide was reduced in ethanol in the presence of a palladium catalyst. Alternatively, zinc–alkali reduction of the epidioxide was shown to yield a triol [now known to be ergosta-6 : 22-diene-3β : 5α : 8α-triol (IX)], which afforded the same ergostenediol on catalytic hydrogenation. Müller suggested later (*Z. physiol. Chem.*, 1935, **231**, 75) that this ergostenediol-I might be an ergost-8(14)-ene-3 : 5-diol; the correct structure is discussed below.

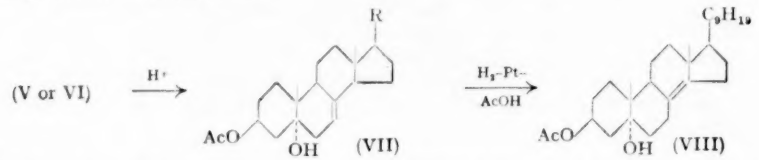


The acetate (I; R = Ac) of ergosterol epidioxide was prepared from ergosteryl acetate by slight modification of the original method of Windaus and Brunken (*Annalen*, 1928, **460**, 225). [In the formulæ the epidioxide bridge is depicted as being in an α-configuration because of the readiness of acetylation of derived 5-hydroxy-steroids (cf. Part LVI), and for a further reason discussed below.] Hydrogenation of (I; R = Ac) in acetic acid with Adams catalyst resulted in the rapid uptake of two mols. of hydrogen, to give the fully saturated epidioxide (II), whereas reduction in neutral solution employing a catalyst derived from a hydrated platinic oxide (cf. Part LVI) afforded a dihydro-compound (III)—these results very closely paralleled those obtained with dehydroergosterol epidioxide. The structure of the dihydro-compound (III) was confirmed by ozonolysis to the aldehyde (IV), together with the corresponding acid.

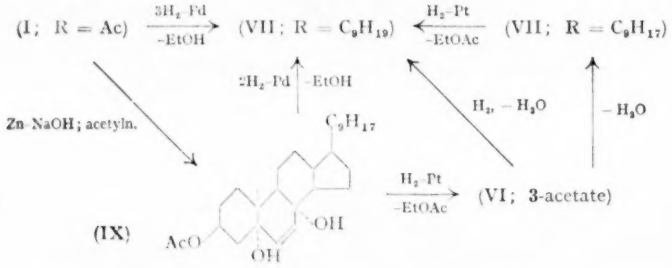
Further hydrogenation of the tetrahydro-acetate (II) in concentrated ethyl acetate solution with Adams catalyst resulted in the uptake of one mol., to produce the 5α : 8α-diol (V)—a behaviour analogous to that observed in the 9 : 11-dehydro-series, except that

* Part LIX, preceding paper.

this saturated glycol was somewhat more soluble and separated only in 60% yield. Hydrogenation of (I; R = Ac) under these conditions gave only a negligible precipitate of the Δ^{22}-5α : 8α-diol (although a good yield of $\Delta^{9(11):22}$-5α : 8α-diol was obtained in the dehydro-series). This side-chain unsaturated diol could be isolated after such experiments by chromatography, but its preparation was best effected by hydrogenating ergosterol epidioxide itself in concentrated ethyl acetate solution, the sparingly soluble triol (VI) then separating rapidly in good yield.



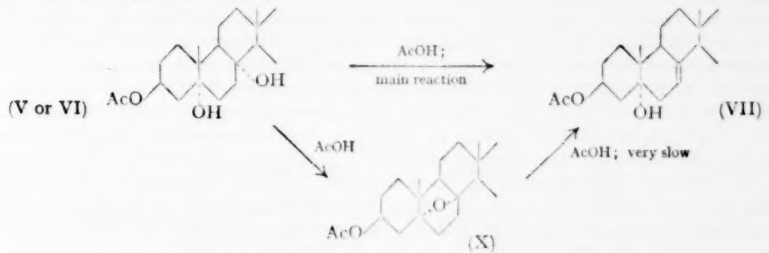
These 5α : 8α-glycols were very readily dehydrated by dilute mineral acids, to yield 5α-hydroxy-Δ^7-steroids (VII; R = C_9H_{17} or C_9H_{19}) (cf. the dehydration of 8α-hydroxy-Δ^9-compounds to 7 : 9-dienes, Part LVI). The structure (VII) was confirmed by (*a*) acetylation to 3β : 5α-diacetates, and (*b*) the infra-red and ultra-violet absorption due to the Δ^7-bond (cf. Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402; Bladon, Henbest, and Wood, *J.*, 1952, 2737). Further, these Δ^7-compounds were converted in high yield into the known $\Delta^{8(14)}$-steroid (VIII) (cf. Part LVI) when shaken in acetic acid with platinum and hydrogen. (Dr. D. H. R. Barton has kindly informed us that the 5-hydroxy-$\Delta^{7:22}$-compound is also obtained by lithium aluminium hydride reduction of ergosterol epidioxide.) The conditions employed for the dehydration of the 8α-hydroxyl group in the 5 : 8-diols are those favouring *trans*-elimination, and thus a kinetically controlled dehydration takes place towards $C_{(7)}$ with loss of the 7β-hydrogen atom, and not towards the $C_{(14)}$ (α-H) (or possibly $C_{(9)}$) position to give a thermodynamically more stable compound. The reaction thus provides further proof for the α-configurations of the 8-hydroxyl group and hence of the epidioxide bridge in compounds (I)—(IV).



As soon as the $\Delta^{8(14)}$-compound (VIII) became available (Part LVI) it was clear that, contrary to Müller's suggestion (*loc. cit.*), the much higher-melting "ergostenediol-I" could not have this structure. The physical constants recorded by the earlier workers were in good agreement with those of the Δ^7-compound (VII; R = C_9H_{19}), and their identity was confirmed on repetition of the Windaus' preparations of the diol. The Windaus reactions, as mentioned earlier, involve hydrogenation either of ergosterol epidioxide ($3H_2$ uptake) or of the $\Delta^{6:22}$-5 : 8-diol (IX) ($2H_2$ uptake), and no doubt proceed *via* a diol (V) or (VI) saturated in ring B; this diol is then dehydrated to a Δ^7-compound in contact with the (acidic) hydrogen adsorbed on the palladium catalyst. However, by use of a platinum catalyst and ethyl acetate as solvent selective reduction of the 6 : 7-bond in (IX) can be achieved, to give the nuclear-saturated glycol (VI). The relationships that have now been established are depicted in the accompanying scheme.

Dehydration of $\Delta^{9(11)}$-5α : 8α-glycols to the corresponding 5α : 8α-epoxides in high yield by 5% acetic acid in boiling acetone has been described in the previous paper. However, when the 5 : 8-diols (V) or (VI) were similarly treated, 80% of the starting material was

recovered together with about 15% of the 5-hydroxy-Δ^7-steroid (VII) and 5% of the 5α : 8α-epoxide (X). Longer reaction times resulted in the dehydration of larger proportions of diol, but the ratio of (VII) to (X) remained approximately constant. These experiments indicated that (VII) and (X) were being formed from the diol by two competing reactions, and that the rate of isomerisation of (X) to the Δ^7-compound must be slow relative to the dehydration reactions. Actually it was found, by separate experiment, that the 5 : 8-oxide was only very slowly isomerised in the acetic acid–acetone medium, although slightly more rapidly in acetic acid alone. Treatment of the oxide with dilute mineral acid rapidly yielded (VII).



Further reactions in the 9 : 11-dehydro-series established that, although the formation of the 5 : 8-oxide corresponding to (X) was the main reaction (in acetic acid–acetone), direct dehydration of the 5 : 8-diol to a 5-hydroxy-7 : 9-diene corresponding to (VII) also took place to a small extent. Conjugated diene was formed more rapidly from the diol than from the $\Delta^{9(11)}$-5 : 8-oxide under the same conditions.

It was evident that each of the three reactions just considered proceeded more rapidly with the Δ^9-compounds than with the nuclear saturated analogues. This is doubtless due to the greater case of fission of the allylic $C_{(8)}$–oxygen bond which has to be broken in each of the reactions of the $\Delta^{9(11)}$-compounds. Dehydration of the 5 : 8-glycols to 5-hydroxy-Δ^7(or $\Delta^{7:9}$)-steroids, catalysed by mineral acid, no doubt proceeds partly *via* the 5 : 8-oxides (similar proportions formed as with acetic acid), but of course further rapid isomerisation occurs under these conditions.

Although perhydrophenanthrene compounds with *trans-anti-cis*-configurations at the ring junctions can readily adopt chair conformations in each ring (cf. Johnson, *Experientia*, 1951, **7**, 315), in the nuclear-saturated 5α : 8α-diol (V) or (VI) the additional *trans*-fused ring D will force either ring B or ring C into a boat conformation. Of these alternatives, the former (*i.e.*, ring B boat, rings A and C chair) appears the more likely, as there is much steric interference between the two angular methyl groups attached to $C_{(10)}$ and $C_{(13)}$ in the other conformation. When ring B is in the boat form, the conformation of the 5 : 8-glycols is that of the ergosterol epidioxide or the 6 : 7-dihydroergosterol epidioxide from which they are derived; in each case the molecule seems relatively unstrained. The 5- and the 8-hydroxyl group are found to be quite close to each other, and thus favourably arranged for forming 5 : 8-oxides. However, in this conformation, the 8α-hydroxyl group is also seem to be polar (with respect to ring B) and coplanar with the 7β-hydrogen atom, thus facilitating dehydration to Δ^7-compounds under acidic conditions, and this becomes the main direction of reaction in the nuclear-saturated compounds. The conformation of steroids with an 8α-substituent (in particular, 3β-acetoxy-8α-ergostan-11-one) will be discussed further in another paper.

Experimental

General experimental directions are given in the previous paper.

3β-Acetoxy-5α : 8α-epidioxyergosta-6 : 22-diene (Ergosteryl Acetate Epidioxide) (I; R = Ac).—Ergosteryl acetate (20 g.) was dissolved in absolute ethanol (3 l.) together with eosin (150 mg.), and the solution was irradiated and heated under reflux by means of a 300-w tungsten-filament lamp placed beneath the flask, while oxygen was bubbled through the solution continuously. Irradiation was stopped when the solution ceased to show a maximum at 2800 Å (about 24 hr.). The product crystallised as plates (10 g.), m. p. 193—200°, when the solution was concentrated

to a small bulk. Two further recrystallisations from chloroform–ethanol gave the epidioxide as flat needles, (8·5 g.), m. p. 199—206°, $[\alpha]_D$ −19° (*c*, 1·0) (Windaus and Brunken, *loc. cit.*, give m. p. 202°, $[\alpha]_D$ −18°). Hydrolysis of the acetate (5·0 g.) with boiling 5% methanolic potassium hydroxide (300 c.c.) for 10 min. gave ergosterol epidioxide, stout needles (4·0 g.) (from ethanol), m. p. 181—185°, $[\alpha]_D$ −36° (*c*, 0·9) (Windaus and Brunken record m. p. 178°, $[\alpha]_D$ −36°).

3β-*Acetoxy*-5α : 8α-*epidioxyergostane* (II).—Ergosteryl acetate epidioxide (1 g.) was shaken in acetic acid (100 c.c.) with hydrogen and prereduced Adams catalyst (50 mg.) until 2 mols. of hydrogen had been absorbed. The solution was filtered and evaporated to dryness under reduced pressure and the residue chromatographed on deactivated alumina (100 g.). Elution with light petroleum–benzene (3 : 1) yielded crystals (0·6 g.), m. p. 185—198°, which gave 3β-*acetoxy*-5α : 8α-*epidioxyergostane* as plates (from methanol) (0·37 g.), m. p. 204—209°, $[\alpha]_D$ −89° (*c*, 1·1) (Found: C, 76·1; H, 10·55. $C_{30}H_{50}O_4$ requires C, 75·9; H, 10·6%). The compound showed no ultra-violet light absorption. Elution with benzene gave a fraction (250 mg.), m. p. 200—225°, which on recrystallisation from methanol afforded 3β-*acetoxyergost*-7-*en*-5α-*ol* (VII; R = C_9H_{19}) as plates, m. p. 224—229°, $[\alpha]_D$ +20° (*c*, 1·0) (Found: C, 78·7; H, 11·1. $C_{30}H_{50}O_3$ requires C, 78·55; H, 11·0%). Light absorption: ε_{2050} 7200; ε_{2100} 4500 (under the same conditions γ-ergostenol exhibited ε_{2050} 6700 and ε_{2100} 4800). This Δ^7-compound is the 3-acetate of "ergostendiol I" (see below); Windaus, Bergmann, and Lüttringhaus (*loc. cit.*) give m. p. 227°, $[\alpha]_D$ +14·7°. Alkaline hydrolysis of (II) gave, after crystallisation from methanol, 5α : 8α-*epidioxyergostan*-3β-*ol* as fine needles, m. p. 175—177°, $[\alpha]_D$ −104° (*c*, 0·75) (Found: C, 77·75; H, 10·9. $C_{28}H_{48}O_3$ requires C, 77·7; H, 11·2%).

Ergost-7-*ene*-3β : 5α-*diol and its Diacetate*.—Prepared by hydrolysis of the 3β-acetate, this *diol* crystallised from ethyl acetate as plates, m. p. 232—240°, $[\alpha]_D$ +16° (*c*, 0·94) (Found: C, 80·6; H, 11·5. $C_{28}H_{48}O_2$ requires C, 80·7; H, 11·6%). This corresponds to "ergostendiol I" (see also below), for which Windaus, Bergmann, and Lüttringhaus record m. p. 234°, $[\alpha]_D$ +14·7°.

3β-Acetoxyergost-7-en-5α-ol (0·5 g.) was heated in chloroform (11·3 c.c.) with acetyl chloride (3·8 c.c.) and dimethylaniline (5·8 c.c.) under reflux for 20 hr. After evaporation to dryness under reduced pressure, the residue was worked up with ether and water. The material extracted by ether was chromatographed on deactivated alumina (50 g.). Elution with benzene–light petroleum (2 : 3) yielded a gum from which the *diacetate* was obtained by crystallisation from methanol as flat needles (280 mg.), m. p. 127·5—129·5°, $[\alpha]_D$ +68° (*c*, 1·0) (Found: C, 76·8; H, 10·35. $C_{32}H_{52}O_4$ requires C, 76·75; H, 10·45%).

3β-*Acetoxyergostane*-5α : 8α-*diol* (V).—3β-Acetoxy-5α : 8α-epidioxyergostane (1 g.) in ethyl acetate (50 c.c.) was shaken in hydrogen with prereduced Adams catalyst (100 mg.). Absorption of hydrogen almost ceased at 43 c.c. (1 mol = 49 c.c.), and the hydrogenation was interrupted. The solution was warmed to redissolve some precipitated 5α : 8α-diol, filtered, and evaporated to dryness under reduced pressure. The residue was chromatographed on deactivated alumina (100 g.), giving 3 principal fractions: (*a*) light petroleum–benzene (3 : 1) eluted starting material (150 mg.), m. p. 205—207°, $[\alpha]_D$ −85° (*c*, 0·6); (*b*) benzene afforded plates (50 mg.), m. p. 224—228°, $[\alpha]_D$ +20° (*c*, 0·7), which gave no m. p. depression on admixture with 3β-acetoxyergost-7-en-5α-ol; (*c*) methanol–ether (1 : 9) gave 3β-*acetoxyergostane*-5α : 8α-*diol* (700 mg.), which crystallised from methanol, containing a little pyridine, as fine needles, m. p. 170—200° (decomp.), $[\alpha]_D$ −43° (*c*, 0·72) (Found: C, 75·3; H, 11·0. $C_{30}H_{52}O_4$ requires C, 75·6; H, 11·0%). The substance showed no ultra-violet light absorption.

Hydrolysis of the 5 : 8-diol 3-acetate with alkali, followed by isolation with ether and crystallisation from methanol, gave *ergostane*-3β : 5α : 8α-*triol*, m. p. 170—180°, $[\alpha]_D$ −50° (*c*, 0·63) (Found: C, 77·05; H, 11·65. $C_{28}H_{50}O_3$ requires C, 77·35; H, 11·6%).

3β-*Acetoxy*-5α : 8α-*epoxyergostane* (X; C_9H_{19} side chain).—3β-Acetoxyergostane-5α : 8α-diol (400 mg.) was heated with 5% acetic acid in acetone (100 c.c.) under reflux for 6 hr. After dilution with water the product was isolated with ether. It was added in the minimum of benzene to deactivated alumina (40 g.). The column was eluted as follows: (*a*) light petroleum (b. p. 60—80°) gave a gum (100 mg.) which, on crystallisation from methanol containing a trace of pyridine, gave the 5α : 8α-*epoxide* as needles (60 mg.), m. p. 99—101°, $[\alpha]_D$ −3° (*c*, 0·5) (Found: C, 78·2; H, 11·0. $C_{30}H_{50}O_3$ requires C, 78·55; H, 11·0%) (the substance showed no ultra-violet light absorption); (*b*) benzene afforded a fraction (260 mg.) giving 3β-acetoxyergost-7-en-5α-ol, m. p. 220—225° (from methanol), $[\alpha]_D$ +18° (*c*, 0·9); (*c*) methanol–ether (1 : 9) eluted 50 mg. of gum which crystallised from methanol to give unchanged 5α : 8α-diol as needles, m. p. 160—190° (decomp.).

Relative Stabilities of 3β-*Acetoxy*-5α : 8α-*epoxyergostane and* 3β-*Acetoxy*-5α : 8α-*epoxyergost*-

9(11)-*ene towards Acetic Acid.*—(i) 3β-Acetoxy-5α : 8α-epoxyergostane (35 mg.) was heated under reflux with 5% acetic acid in acetone (10 c.c.) for periods up to 16 hr. The steroid was then recovered with ether in the usual way and chromatographed on 5 g. of deactivated alumina. The material was recovered unchanged (m. p. 98—99°).

The saturated 5α : 8α-epoxide (33 mg.) was dissolved in glacial acetic acid (10 c.c.) and kept overnight at 20°. The product was worked up with ether and chromatographed on 5 g. of deactivated alumina. Two fractions were eluted: (*a*) benzene–light petroleum (1 : 4) gave the epoxide as a gum (28 mg.), which crystallised as needles, m. p. 97—100°; (*b*) ether–methanol (9 : 1) gave a solid (4 mg.), m. p. 190—208°, which crystallised from ethyl acetate as flakes, m. p. 210—220°, corresponding to the Δ^7-5α-hydroxy-compound. The conversion into the Δ^7-isomer in this experiment is thus of the order of 12—15%.

(ii) 3β-Acetoxy-5α : 8α-epoxyergost-9(11)-ene was treated with 5% acetic acid in acetone, as in the experiments with the saturated 5α : 8α-epoxide. The product was isolated with ether, and the conversion into $\Delta^{7:9(11)}$-diene estimated by light-absorption measurements. The results after varying reaction times were as follows [ε being assumed to be 16,000 at 2420 Å for the pure 5α-hydroxy-7 : 9(11)-diene] :

Time (hr.)	ε_{2420}	Conversion (%)	Time (hr.)	ε_{2420}	Conversion (%)
2	—	—	16	1300	*ca.* 8
4½	450	2—3	14 in AcOH at 20°	3000	*ca.* 20

3β-Acetoxyergost-9-ene-5α : 8α-diol (115 mg., shown by ultra-violet measurements to be free from 7 : 9-diene) was heated under reflux with 5% acetic acid in acetone (10 c.c.) for 1 hr. Isolation with ether followed by chromatography afforded the 5 : 8-oxide fraction (100 mg.) (eluted with light petroleum, and obtained pure by crystallisation from methanol, cf. previous paper). Further elution with ether gave a semi-solid product (14 mg.; ε 9000, corresponding to 8% of 7 : 9-diene), which on crystallisation gave plates, m. p. 210—220°.

3β-*Acetoxyergost-7-en-5α-ol* (VII; R = C_9H_{19}) *from* 3β-*Acetoxy-5α : 8α-epoxyergostane.*—The epoxide (50 mg.) was dissolved in methanol (5 c.c.) and a trace of concentrated hydrochloric acid added. Agitation produced an immediate precipitate of minute plates which on recrystallisation from methanol gave flat needles (20 mg.), m. p. and mixed m. p. 224—227°, $[\alpha]_D$ +18° (*c*, 0·6).

Ergost-22-ene-3β : 5α : 8α-triol (VI).—Ergosterol epidioxide (1 g.) in the minimum volume of ethyl acetate was shaken in hydrogen with prereduced Adams catalyst (100 mg.). A dense white precipitate of the triol, in the form of fine needles, quickly began to separate, the uptake of hydrogen becoming gradually slower until it had virtually ceased after 93 c.c. (2 mols. = 99 c.c.). The product was removed by filtration, washed with a little ethyl acetate, and dried (yield, 850 mg.; m. p. 182—192°). This material without further purification was in general used for the preparation of the 5α : 8α-epoxide (see below). A sample, crystallised twice from methanol containing a trace of pyridine, gave the *triol* as flat needles, m. p. 202—215°, $[\alpha]_D$ −65° (*c*, 0·67) (Found: C, 77·9; H, 11·5. $C_{28}H_{48}O_3$ requires C, 77·7; H, 11·2%). No ultra-violet-light absorption could be detected.

Dehydration of Ergost-22-ene-3β : 5α : 8α-triol in Mineral Acid to give Ergosta-7 : 22-diene-3β : 5α-diol.—The triol (200 mg.) was dissolved in the minimum volume of methanol and a trace of hydrochloric acid added to the cooled solution. The *diol*, precipitated as platelets (140 mg.), m. p. 220—230°, recrystallised from *iso*propyl alcohol as plates (50 mg.), m. p. 227—234°, $[\alpha]_D$ +1° (*c*, 0·5) (Found: C, 80·55; H, 10·8. $C_{28}H_{46}O_2$ requires C, 81·05; H, 11·2%). Acetic anhydride–pyridine at 20° gave 3β-*acetoxyergosta-7 : 22-dien-5α-ol* (VII; R = C_9H_{17}) (flat needles from ethyl acetate), m. p. 228—233°, $[\alpha]_D$ +2° (*c*, 0·7) (Found: C, 78·7; H, 10·45. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%). Acetylation of the monoacetate by acetyl chloride–dimethylaniline yielded 3β : 5α-diacetoxyergosta-7 : 22-diene, which after chromatography and recrystallisation from methanol formed needles, m. p. 158·5—161°, $[\alpha]_D$ +51° (*c*, 0·6) (Found: C, 77·2; H, 10·15. $C_{32}H_{50}O_4$ requires C, 77·0; H, 10·1%).

3β *Acetoxyergost-7-en-5α-ol and -8(14)-ene* (VIII) *from* 3β-*Acetoxyergosta-7 : 22-dien-5α-ol.*—The diene (400 mg.) was dissolved in ethyl acetate (150 c.c.) and shaken in hydrogen with Adams catalyst (50 mg.) until no further uptake of hydrogen occurred. The solution was filtered and evaporated until the product separated as plates, m. p. 215—225°. Recrystallisation from ethyl acetate gave 3β-acetoxyergost-7-en-5α-ol as plates (100 mg.), m. p. and mixed m. p. 224—228°, $[\alpha]_D$ +16° (*c*, 1·0).

A solution of the diene (200 mg.) in acetic acid (25 c.c.) was shaken with hydrogen in the

presence of Adams catalyst (50 mg.) for 9 hr.; 1 mol. of hydrogen was rapidly absorbed, the shaking being prolonged in order to achieve complete isomerisation of the nuclear double bond. Recrystallisation of the product from methanol gave 3β-acetoxyergost-8(14)-en-5α-ol (VIII), m. p. and mixed m. p. with an authentic sample, 160—163°, $[\alpha]_D$ −1·5° (*c*, 0·78).

3β-*Acetoxy*-5α : 8α-*epoxyergost*-22-*ene* (X; C_8H_{17} side chain).—Ergost-22-ene-3β : 5α : 8α-triol (2·0 g.) was heated under reflux for 6 hr. with 5% acetic acid in acetone (400 c.c.). The product, isolated with ether, was acetylated by treatment overnight in pyridine (20 c.c.) with acetic anhydride (10 c.c.) at 20°. The product was isolated with ether and passed in benzene solution on to deactivated alumina (200 g.). Elution with light petroleum–benzene (4 : 1) yielded fractions: (*a*) (100 mg.) which crystallised from methanol as fine needles, m. p. 112—114·5°, $[\alpha]_D$ +25° (*c*, 0·98) (this material remains unidentified); (*b*) a gum (100 mg.) from which, on crystallisation from methanol, 3β-*acetoxy*-5α : 8α-*epoxyergost*-22-*ene* was obtained as needles (60 mg.), m. p. 133—136°, $[\alpha]_D$ −35° (*c*, 1·0) (Found: C, 78·6; H, 10·45. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%). Further elution with light petroleum–benzene (1 : 1) afforded crystals (630 mg.) which, after 3 crystallisations from ethyl acetate, gave 3β-acetoxyergosta-7 : 22-dien-5α-ol as platelets (100 mg.), m. p. (and mixed m. p.) 222—230°, $[\alpha]_D$ +2° (*c*, 1·0). Finally, methanol–ether (1 : 9) eluted a gum (1·2 g.) from which 3β-*acetoxyergost*-22-*ene*-5α : 8α-*diol* was obtained as small needles (from methanol), m. p. 190—195° (becoming lower on recrystallisation), $[\alpha]_D$ −61·5° (*c*, 0·75) (Found: C, 76·1; H, 10·7. $C_{30}H_{50}O_4$ requires C, 75·9; H, 10·6%).

3β-*Acetoxyergost*-22-*ene*-5α : 8α-*diol from Ergosta*-6 : 22-*diene*-3β : 5α : 8α-*triol* (IX) ("*Ergostadiene-triol* I").—Ergosta-6 : 22-diene-3β : 5α : 8α-triol was prepared in 60% yield, as described by Windaus *et al.* (*Annalen*, 1928, **465**, 148; 1929, **472**, 195) by treatment of ergosteryl acetate epidioxide with zinc and alkali. It had m. p. 215—225°, $[\alpha]_D$ −15° (*c*, 0·3) (the above authors give m. p. 227°, $[\alpha]_D$ −13·7°) (Found: C, 77·75; H, 10·9. Calc. for $C_{28}H_{46}O_3$: C, 78·1; H, 10·75%). The triol (300 mg.) was acetylated by treatment overnight with pyridine and acetic anhydride, and the crude product, after working up *via* ether, was shaken in hydrogen with prereduced Adams catalyst (50 mg.) and ethyl acetate (70 c.c.). Absorption of 17 c.c. of hydrogen (1 mol.) was rapid, the rate then slackening. The hydrogenation was interrupted at this point, the catalyst removed, and the solution evaporated to dryness under reduced pressure. The residue was passed in benzene on to deactivated alumina (40 g.) from which further washing with benzene eluted 70 mg. of solid (presumed 5α-hydroxy-Δ^7-material) which was discarded. The remainder of the material was recovered from the column by elution with methanol–ether (1 : 4), giving a solid (270 mg.), which after two recrystallisations from methanol gave 3β-acetoxyergost-22-ene-5α : 8α-diol as needles (60 mg.), m. p. 165—180°, $[\alpha]_D$ −61° (*c*, 0·6). The compound showed no lowering of m. p. on being mixed with an authentic sample (previous experiment) of similar m. p. (168—185°).

3β-*Acetoxyergosta*-7 : 22-*dien*-5α-*ol from* 3β-*Acetoxy*-5α : 8α-*epoxyergost*-22-*ene*.—The Δ^{22}-5α : 8α-epoxide (50 mg.) was dissolved in methanol (2 c.c.), and a trace of hydrochloric acid added. A precipitate of minute needles, m. p. 200—220°, was produced. Two recrystallisations from ethyl acetate gave 3β-acetoxyergosta-7 : 22-dien-5α-ol as small, flat needles, m. p. and mixed m. p. 222—230°, $[\alpha]_D$ +3° (*c*, 0·54).

3β-*Acetoxyergost*-7-*en*-5α-*ol from Ergosteryl Acetate Epidioxide*.—Ergosteryl acetate epidioxide (500 mg.) (in ethanol) was shaken with palladium black in hydrogen until 3 mols. had been absorbed. After filtration, the solution was evaporated to dryness. Chromatography of the residue on deactivated alumina (50 g.) gave a solid (250 mg.), m. p. 212—219°, eluted with benzene, which, after two recrystallisations from *iso*propyl alcohol, yielded 3β-acetoxyergost-7-en-5α-ol, m. p. and mixed m. p. 225—229°, $[\alpha]_D$ +18° (*c*, 1·0).

Ergost-22-*ene*-3β : 5α : 8α-*triol from* 5α : 8α-*Epidioxyergost*-22-*en*-3β-*ol*.—The sterol (1 g.; see next experiment) was shaken in the minimum amount of ethyl acetate with prereduced Adams catalyst (50 mg.) in hydrogen. The uptake almost ceased after the absorption of 1 mol. by which time the greater part of the triol (0·8 g.) had been precipitated as fine needles, m. p. 180—185°. Recrystallisation from methanol–pyridine gave material, m. p. 195—202°, $[\alpha]_D$ −67° (*c*, 1·0), showing no m. p. depression on admixture with an authentic sample, m. p. 202—215°.

3β-*Acetoxy*-5α : 8α-*epidioxyergost*-22-*ene* (III).—Ergosteryl acetate epidioxide (5·0 g.) was shaken in ethyl acetate (300 c.c.) in hydrogen together with prereduced yellow, hydrated platinum oxide (50 mg.) until 1·2 mols. of hydrogen had been absorbed. The catalyst was removed, the solution evaporated under reduced pressure, and the residue chromatographed on alumina (300 g.). Elution with benzene gave the *dihydro-acetate* (3·0 g.), plates (from ethanol) (2·3 g.), m. p. 209—215°, $[\alpha]_D$ −121° (*c*, 1·1) (Found: C, 75·95; H, 10·25. $C_{30}H_{48}O_4$ requires

C, 76·2; H, 10·25%). Hydrolysis of this in the usual manner afforded 5α : 8α-*epidioxyergost*-22-*en*-3β-*ol*, matted needles (from methanol), m. p. 175—177°, $[\alpha]_D$ −137° (*c*, 1·4) (Found: C, 77·85; H, 10·8. $C_{28}H_{46}O_3$ requires C, 78·1; H, 10·75%).

3β-*Acetoxy*-5α : 8α-*epidioxybisnorcholan*-22-*al* (IV) *and Methyl* 3β-*Acetoxy*-5α : 8α-*epidioxybisnorcholanate*.—3β-Acetoxy-5α : 8α-epidioxyergost-22-ene (2·0 g.) was dissolved in ethyl acetate (100 c.c.) and cooled to −65°. A saturated solution of ozone in ethyl acetate at −70° was added until a blue colour persisted. The solution, after having attained room temperature, was shaken with ferrous sulphate solution until no further ozone reaction (starch–iodide) was obtained. The solution was washed free from iron salts and shaken with cold aqueous 2% potassium hydroxide to extract acids (see below). The ethyl acetate solution was washed until alkali-free, dried, and evaporated to dryness under reduced pressure. The residue (1·8 g.) was passed in benzene on to deactivated alumina (100 g.). Elution with benzene afforded solid (800 mg.), m. p. 170—190°. Several recrystallisations from *iso*propyl ether gave 3β-*acetoxy*-5α : 8α-*epidioxybisnorcholan*-22-*al* as triangular plates (200 mg.), m. p. 189—199° (decomp.), $[\alpha]_D$ −113° (*c*, 1·0) (Found: C, 71·05; H, 8·85. $C_{24}H_{36}O_5$ requires C, 71·25; H, 9·0%). This gave a yellow gelatinous 2 : 4-dinitrophenylhydrazone.

The alkaline extract was acidified and the precipitated acid taken up in ether. The ethereal layer was evaporated to dryness under reduced pressure, affording a solid (300 mg.), which was crystallised once from ethyl acetate. The acid and ethereal diazomethane gave the *methyl* ester, plates (50 mg.) (from methanol), m. p. 190—195°, $[\alpha]_D$ −120° (*c*, 1·0) (Found: C, 68·85; H, 8·95. $C_{25}H_{38}O_6$ requires C, 69·1; H, 8·8%).

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THE UNIVERSITY, MANCHESTER, 13. [*Received, February 27th*, 1953.]

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411. *The Preparation and Dehydration of* 2-*Methyl*-6-*phenylheptan*-3-*ol*.

By D. H. HEY, JOHN HONEYMAN, D. H. KOHN, and W. J. PEAL.

Dehydration of 2-methyl-6-phenylheptan-3-ol with different reagents gave 2-methyl-6-phenylhept-2-ene, with minor amounts of the hept-3-ene. Reaction of the alcohol with hydrobromic acid followed by dehydrobromination yielded the hept-2-ene.

As a preliminary step in an investigation into the regulated degradation of sterol side-chains the preparation of 2-methyl-6-phenylheptan-3-ol (I) was undertaken. This compound has the same side-chain as 24-hydroxycholesterol. The alcohol was prepared from styrene, which was converted into 1-bromoethylbenzene and thence into 1-phenylethylmalonic acid; decarboxylation of the latter gave β-phenylbutyric acid which was reduced to 3-phenylbutan-1-ol and then converted successively into 1-bromo-3-phenylbutane and, by a Grignard reaction with *iso*butaldehyde, into 2-methyl-6-phenylheptan-3-ol (I). The various stages in this synthesis were accomplished by standard reactions. All the compounds are liquids and no crystalline derivative of the desired alcohol, which has two asymmetric carbon atoms, was obtained. However, oxidation gave 2-methyl-6-phenylheptan-3-one, which was characterised as the crystalline 2 : 4-dinitrophenylhydrazone.

Simonsen and his co-workers (*J.*, 1939, 1504) showed that (−)-α-curcumene consists of a mixture of 2-methyl-6-*p*-tolylhept-1- and -2-ene. This mixture was prepared in an optically inactive form by Carter, Simonsen, and Williams (*J.*, 1940, 451) from 2-methyl-6-*p*-tolylheptan-2-ol, which was synthesised in a manner not unlike that used in the present work. This alcohol was dehydrated with potassium hydrogen sulphate to a mixture of the hept-1-ene and the hept-2-ene with the former predominating.

The dehydration of 2-methyl-6-phenylheptan-3-ol has now been studied using a number of reagents. Comparatively few extensive studies on the dehydration of secondary alcohols of the type $(CH_3)_2CH{\cdot}CH(OH){\cdot}CH_2R$ are found in the literature. Tuot (*Compt. rend.*, 1940, **211**, 561) dehydrated a number of secondary alcohols including 2-methylheptan-3-ol with anhydrous copper sulphate and concluded that where the hydroxyl

group is adjacent to a tertiary carbon atom, dehydration takes place exclusively towards that atom. Henne and Matuszak (*J. Amer. Chem. Soc.*, 1944, **66**, 1649) dehydrated several alcohols by various methods and investigated the products by ozonolysis. One of the compounds they studied was 2-methylpentan-3-ol, from which three isomeric pentenes were obtained. The results show that none of the methods employed gives a single isomer, but that, in general, but not invariably, dehydration favours the formation of 2-methylpent-2-ene rather than 4-methylpent-2-ene. The chief course of the dehydration again involves the tertiary carbon atom.

In selecting methods for the dehydration of 2-methyl-6-phenylheptan-3-ol (I), it was borne in mind that the reagents used must be capable of being applied to 24-hydroxycholesterol. Of the two most likely products 2-methyl-6-phenylhept-2-ene (II) will give on ozonolysis acetone and 3-phenylvaleraldehyde, whereas 2-methyl-6-phenylhept-3-ene (III) will give *iso*butaldehyde and 2-phenylbutaldehyde. The 2 : 4-dinitrophenylhydr-

$Ph{\cdot}CH(CH_3){\cdot}CH_2{\cdot}CH_2{\cdot}CH(OH){\cdot}CH(CH_3)_2$ (I)

$Ph{\cdot}CH(CH_3){\cdot}CH_2{\cdot}CH_2{\cdot}CH{:}C(CH_3)_2$ (II)

$Ph{\cdot}CH(CH_3){\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH(CH_3)_2$ (III)

$Ph{\cdot}C(CH_3){:}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH(CH_3)_2$ (IV)

azones of these carbonyl compounds were readily separated by chromatography on alumina so that each could be estimated. In this way the approximate yields of the heptenes given in the Table were obtained.

When potassium hydrogen sulphate was used for dehydration two treatments were necessary for complete reaction. The use of phosphoric oxide in benzene resulted in the formation of a complex mixture. On ozonolysis acetone and acetophenone were obtained, indicating the presence of 6-methyl-2-phenylhept-2-ene (IV) as well as 2-methyl-6-phenylhept-2-ene (II).

The product obtained by treating 2-methyl-6-phenylheptan-3-ol (I) with hydrobromic acid was shown by analysis to have lost hydrogen bromide during distillation. Completion of the dehydrobromination with collidine gave 2-methyl-6-phenylhept-2-ene (II), identified

Method	2-Methyl-6-phenylheptenes obtained
Anhyd. $KHSO_4$ at 160°	Hept-2-ene, 90% Hept-3-ene, 10%
$KHSO_4$ in boiling xylene	Hept-3-ene, 20% Hept-2-ene, 80%
P_2O_5 in boiling benzene	Hept-2-ene, 70% Hept-5-ene, 30%
$POCl_3$ in boiling pyridine	Hept-2-ene
Reaction with HBr, followed by dehydrobromination	Hept-2-ene

by conversion on ozonolysis into acetone and a phenylvaleraldehyde, isolated as 2 : 4-dinitrophenylhydrazones. No reference has been found in the literature to this aldehyde, but from analysis and the mode of formation it must be 3-phenylvaleraldehyde. It differs from 4-phenylvaleraldehyde prepared by Braun and Kruber (*Ber.*, 1912, **45**, 399).

The results obtained during the present work substantiate the general conclusions of Tuot (*loc. cit.*) and of Henne and Matuszak (*loc. cit.*) that in secondary alcohols of this type dehydration chiefly involves the elimination of hydrogen from the tertiary carbon atom.

Experimental

Solutions in organic solvents which are described as having been washed and dried were washed with dilute sulphuric acid and/or aqueous sodium carbonate (5%), then with water, and dried (Na_2SO_4 or $CaCl_2$).

Ethyl 1-Phenylethylmalonate.—1-Bromoethylbenzene, b. p. 77°/5 mm., was prepared by Ashworth and Burkhardt's method (*J.*, 1928, 1796).

Anhydrous ethanol (250 ml.) was added to sodium (11·5 g., 1 mol.) and when the sodium had dissolved the solution was refluxed for 5 min. (moisture excluded throughout). After the addition of ethyl malonate (80 g., 1 mol.), 1-bromoethylbenzene (90 g., 1 mol.) was dropped in so that the solution boiled gently. After addition was complete, boiling under reflux was continued for 5 hr. When cold, sodium bromide was filtered off and excess of alcohol was evapor-

ated. The solution was diluted with water and extracted with ether. The ethereal extracts were washed, dried, and concentrated. The residue was fractionated and yielded ethyl 1-phenylethylmalonate (100 g., 78%), b. p. 156—157°/7 mm. Fischer and Schmidt (*Ber.*, 1906, **39**, 351) record b. p. 185—187°/24 mm.

Ethyl β-Phenylbutyrate.—1-Phenylethylmalonic acid (40·6 g.), m. p. 141—143°, prepared by hydrolysis of the above ester with aqueous-alcoholic potassium hydroxide, was heated at 180—190° for 30 min. Distillation under reduced pressure yielded β-phenylbutyric acid (30 g., 93%), b. p. 168°/17 mm., m. p. 36—38·5°. Rupe (*Annalen*, 1909, **369**, 323) records m. p. 39—40°.

This acid (35 g.) with concentrated sulphuric acid (2 ml.) in ethanol (100 ml.) at the b. p. (2 hr.) gave the ethyl ester (35 g., 85%), b. p. 128—131°/15 mm. B. p. 111°/4 mm. has been recorded for this ester (Levene and Marker, *J. Biol. Chem.*, 1931, **46**, 1266)

3-Phenylbutan-1-ol.—(*a*) Ethyl β-phenylbutyrate (20 g.) in anhydrous ethanol (100 ml.) was added dropwise to a fine suspension of molten sodium in warm toluene at a rate sufficient to maintain boiling (moisture excluded). Boiling under reflux was continued for 2 hr. after addition was complete. Ethanol (100 ml.) was then added to dissolve excess of sodium, and the solution was poured into water (300 ml.). The usual methods gave recovered β-phenylbutyric acid (1 g.) and 3-phenylbutanol (9·5 g., 64%), b. p. 121—122°/10 mm. Braun, Grabowski, and Kirschbaum (*Ber.*, 1913, **46**, 1266) give b. p. 134°/16 mm.

(*b*) β-Phenylbutyric acid (82 g.) in ether (400 ml.) was added to lithium aluminium hydride (22 g.) in ether (400 ml.) at a rate sufficient to maintain boiling (moisture excluded). The reactants were stirred for 30 min. after completion of the addition, and water (100 ml.) was dropped in followed by sulphuric acid (800 ml., 10%). Material from the ethereal layer, when distilled, gave 3-phenylbutanol (69·5 g., 93%), b. p. 138°/21 mm.

This (1 ml.) in dry pyridine (5 ml.) was added to 3 : 5-dinitrobenzoyl chloride (1 g.) in dry benzene (10 ml.) and left at room temperature for 18 hr. Thus was obtained *3-phenylbutyl 3 : 5-dinitrobenzoate*, m. p. 73—74° (from alcohol) (Found : C, 59·6; H, 4·6; N, 8·1. $C_{17}H_{16}O_6N_2$ requires C, 59·3; H, 4·7; N, 8·1%).

1-Bromo-3-phenylbutane.—(*a*) This compound, prepared from 3-phenylbutanol by Levene and Marker's method (*loc. cit.*) with phosphorus tribromide, had b. p. 117—118°/14 mm.

(*b*) 3-Phenylbutanol (15 g.) was refluxed with aqueous hydrobromic acid (21 g., 48%) and concentrated sulphuric acid (7 g.) for 3 hr. When cold the heavy bromo-compound was separated, washed with concentrated sulphuric acid (2 ml.), then with water, and dissolved in ether. The ethereal solution, after being washed and dried, was concentrated. The residual oil was fractionated, giving 1-bromo-3-phenylbutane (16 g., 75%), b. p. 127—128°/21 mm. Levene and Marker record b. p. 120°/17 mm. for this compound.

2-Methyl-6-phenylheptan-3-ol.—Approx. one-fifth of a solution of 1-bromo-3-phenylbutane (24·5 g., 1 mol.) in dry ether (30 ml.) was added to magnesium turnings (3 g., 1 mol.) and a few crystals of iodine (moisture excluded). After gentle warming to start the reaction dry ether (60 ml.) was added, followed gradually by the remainder of the ethereal solution of 1-bromo-3-phenylbutane. After 20 min.' boiling the reactants were cooled to 0° and a solution of *iso*butaldehyde (9 g., 1 mol.) in dry ether (25 ml.) was dropped in. After a further hr.' stirring the ethereal solution was poured on ice-water (600 ml.) containing ammonium chloride (40 g.). The ethereal layer was separated and the aqueous phase was extracted with ether. The combined ethereal extracts were washed with water, dried, and concentrated. The residue gave a main fraction (18·1 g., 76·5%), b. p. 132—159°/14 mm. Refractionation of this gave *2-methyl-6-phenylheptan-3-ol* (10·6 g.), b. p. 146—150°/12 mm., n_D^{15} 1·5045 (Found : C, 81·6; H, 10·8. $C_{14}H_{22}O$ requires C, 81·5; H, 10·7%).

Attempts to prepare the 3 : 5-dinitrobenzoate, the phenylurethane, and the α-naphthylurethane of 2-methyl-6-phenylheptan-3-ol did not yield solid compounds.

2-Methyl-6-phenylheptan-3-one.—2-Methyl-6-phenylheptan-3-ol (2·1 g.) in benzene (10 ml.) was added gradually to sodium dichromate (1·9 g.) dissolved in sulphuric acid (1·7 g.) and water (10 ml.). When the reaction mixture was cold it was poured into water and extracted with ether. The ethereal extracts gave *2-methyl-6-phenylheptan-3-one* (1·3 g., 62%), b. p. 145—146°/12 mm., n_D^{20} 1·4997 (Found : C, 82·0; H, 9·5. $C_{14}H_{20}O$ requires C, 82·3; H, 9·8%). This afforded a *2 : 4-dinitrophenylhydrazone*, m. p. 89—90° (Found : C, 61·9; H, 6·3; N, 14·8. $C_{20}H_{24}O_4N_4$ requires C, 62·5; H, 6·3; N, 14·6%).

Examination of the Products obtained on the Dehydration of 2-Methyl-6-phenylheptan-3-ol.—The products from the dehydration methods described below were examined by a common method.

A slight excess of ozone was passed into a solution of the products of dehydration in acetic acid. The solution was poured into water and distilled from zinc dust (2 g.). The first three fractions (10 ml.) were each treated with 2 : 4-dinitrophenylhydrazine (0·5 g.) in acetic acid (15 ml.). The resultant 2 : 4-dinitrophenylhydrazones were separated by chromatography from benzene on alumina.

In a trial experiment a benzene solution of acetone 2 : 4-dinitrophenylhydrazone (0·29 g.) and *iso*butaldehyde 2 : 4-dinitrophenylhydrazone (0·18 g.) was chromatographed on alumina (100 g.). As no separation into bands occurred on development of the chromatogram, isolation of the dinitrophenylhydrazones was achieved by continuous elution with benzene. *iso*Butaldehyde dinitrophenylhydrazone (0·18 g., 100%) was obtained from the first fractions (140 ml.), and acetone dinitrophenylhydrazone (0·24 g., 83%) from the later fractions (280 ml.).

Dehydration of 2-Methyl-6-phenylheptan-3-ol.—(a) 2-Methyl-6-phenylheptan-3-ol (3·2 g.) was heated for 2 hr. with powdered, freshly fused potassium hydrogen sulphate at 150—160°/100 mm. under dry nitrogen. Water distilled off at first, followed by an oil. After cooling, the residue was extracted with ether and the extracts were combined with the distillate. The ethereal solution was washed and dried. The ether was evaporated and the residue distilled under reduced pressure. Redistillation gave a main fraction, b. p. 118—120°/16·5 mm., n_D^{16} 1·5018 (1·8 g., 62%) (Found : C, 89·0; H, 10·5. $C_{14}H_{20}$ requires C, 89·3; H, 10·7%). Two other attempted dehydrations under similar conditions resulted in products which were incompletely dehydrated.

2-Methyl-6-phenylheptan-3-ol (9 g.) was heated for 2 hr. with powdered freshly fused potassium hydrogen sulphate (40 g.) at 150—160°/80 mm. in an atmosphere of nitrogen. The product, isolated as in the previous experiment but not distilled, was heated with fresh potassium hydrogen sulphate (40 g.) under the same conditions for 1½ hr. more. The product isolated as above was separated by distillation into five fractions : (1) (0·5 g.), b. p. 100—118°/16 mm., n_D^{20} 1·5005; (2) (1·5 g.), b. p. 121—124°/16 mm., n_D^{20} 1·5007; (3) (2·85 g.), b. p. 125—128°/16 mm., n_D^{20} 1·5010; (4) (0·55 g.), b. p. 128—130°/16 mm., n_D^{20} 1·5010; (5) (0·5 g.), b. p. 130—135°/16 mm., n_D^{20} 1·5019. Fractions 1—4 (5·4 g., 68%) were combined and part (0·28 g.) was examined by the general method which has been described. The products were *iso*butaldehyde 2 : 4-dinitrophenylhydrazone (0·025 g.; m. p. 179—180°) and acetone 2 : 4-dinitrophenylhydrazone (0·185 g.; m. p. 118—121°).

(b) *With anhydrous potassium hydrogen sulphate in xylene.* A solution of 2-methyl-6-phenylheptan-3-ol (0·9 g.) in xylene (5 ml.) was boiled under reflux for 18 hr. with potassium hydrogen sulphate (24 g.). The mixture was extracted with ether and the ethereal extracts were washed and dried. The solvents were evaporated by maintaining the residue at 100°/50 mm. The crude heptene (0·55 g.), examined by the general method described, yielded a 2 : 4-dinitrophenylhydrazone (0·31 g.), which on separation gave *iso*butaldehyde 2 : 4-dinitrophenylhydrazone (0·070 g., m. p. 176—179°) and acetone 2 : 4-dinitrophenylhydrazone (0·24 g., m. p. 121—123°).

(c) *With phosphoric oxide in benzene.* 2-Methyl-6-phenylheptan-3-ol (4·1 g.) in dry benzene (25 ml.) was boiled under reflux for 3 hr. with phosphoric oxide (5 g.). There was much frothing and the solid became discoloured. When cold the solution was decanted and the residue treated with water and extracted with ether. The combined benzene and ether solutions were washed, dried, and evaporated. The residue was separated into fractions (1) (0·1 g.), b. p. 40—120°/15 mm., n_D^{15} 1·5090, (2) (0·3 g.), b. p. 120—124°/15 mm., n_D^{15} 1·5110, (3) (1·7 g.), b. p. 125—127°/15 mm., n_D^{15} 1·5131, and (4) (0·45 g.), b. p. 160—230°/16 mm., n_D^{15} 1·5150 ⟶ 1·5226. Fractions (2) and (3) (2 g., 50%) contained the heptenes (Found : C, 88·8; H, 11·0%).

Fraction (3) (0·33 g.), examined by the general method, yielded crude 2 : 4-dinitrophenylhydrazones (0·48 g.), a part of which (0·19 g.) was separated by chromatography into acetophenone 2 : 4-dinitrophenylhydrazone (0·06 g.), m. p. 237—240°, mixed m. p. with an authentic specimen (m. p. 244—247°) 237—242°, and acetone 2 : 4-dinitrophenylhydrazone (0·13 g.), m. p. 121—123°.

(d) *With phosphorus oxychloride in pyridine.* A solution of 2-methyl-6-phenylheptan-3-ol (0·74 g.) in pyridine (50 ml.) was boiled under reflux for 3 hr. with phosphorus oxychloride (8 ml.) and then left overnight at room temperature. The solution was poured into ice-water (300 ml.) containing concentrated hydrochloric acid (50 ml.). The oil which separated was dissolved in ether and the ethereal solution washed and evaporated. Part (0·31 g.) of the residual oil (0·62 g.), examined by the usual procedure, gave a 2 : 4-dinitrophenylhydrazone (0·1 g.), which, on purification by chromatography, was shown to be acetone 2 : 4-dinitrophenylhydrazone, m. p. 118—121°. A trace of a 2 : 4-dinitrophenylhydrazone, more soluble in benzene, was obtained from the second fraction obtained by chromatography and this, on further

chromatography and recrystallisation from ethanol, was established to be **3-*phenylvaleraldehyde* 2 : 4-*dinitrophenylhydrazone***, m. p. 90—91° (Found : C, 59·2; H, 5·4; N, 16·0. $C_{17}H_{18}O_4N_4$ requires C, 59·6; H, 5·3; N, 16·4%).

It is concluded that this dehydration produced 2-methyl-6-phenylhept-2-ene.

Attempted Preparation of **3-*Bromo*-2-*methyl*-6-*phenylheptane***.—Phosphorus tribromide (5 g.) was added to 2-methyl-6-phenylheptan-3-ol (4·2 g.) at 0° and the mixture heated on a steam-bath for an hour. When cold the mixture was poured into ice-water, and the heavy product which separated was dissolved in ether, washed, and dried. Evaporation and distillation gave a main fraction (2·5 g.), b. p. 130—133°/17 mm., n_D^{15} 1·5091 (Found : C, 82·8; H, 9·9; Br, 9·2. Calc. for $C_{14}H_{21}Br$: C, 62·4; H, 7·8; Br, 29·7%). On redistillation the product had an even lower bromine content (Found : C, 88·9; H, 10·4; Br, 3·92%), suggesting that further dehydrobromination had taken place

Preparation of **2-*Methyl*-6-*phenylhept*-2-*ene***.—Dehydrobromination of the bromo-compound (1·7 g.) obtained in the previous experiment was completed by boiling it under reflux in collidine (5 ml.) under nitrogen. After 5 min. collidine hydrobromide had separated. When cold the solution was dissolved in ether and then dried. After evaporation collidine (5 ml.) was added to the residue and the solution boiled under reflux (nitrogen) for 2 hr. When cold, the collidine solution was treated as before. The residue (1·3 g.) was fractionated, giving **2-*methyl*-6-*phenylhept*-2-*ene*** (1·1 g.), b. p. 117—119°/12 mm., n_D^{20} 1·5020 (Found : C, 89·6; H, 10·6. $C_{14}H_{20}$ requires C, 89·3; H, 10·7%). The product was examined in the usual way and the resulting 2 : 4-dinitrophenylhydrazones were separated into acetone 2 : 4-dinitrophenylhydrazone (m. p. 121—123°), and 3-phenylvaleraldehyde 2 : 4-dinitrophenylhydrazone which after recrystallisation from ethanol had m. p. 93—94°, undepressed on admixture with the compound prepared previously.

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412. *Structural Chemistry of the Alkoxides. Part IV.* Normal Alkoxides of Silicon, Titanium, and Zirconium.*

By D. C. BRADLEY, R. C. MEHROTRA, J. D. SWANWICK, and W. WARDLAW.

The normal alkoxides, $Ti(OC_nH_{2n+1})_4$ where n = 2, 3, 4, 5, 6, 7, and 8, and $Zr(OC_nH_{2n+1})_4$ where n = 2, 3, 4, 5, 6, and 8, have been prepared and their molecular weights and boiling points measured. Molecular complexity is practically independent of chain length while boiling points increase linearly with molecular weight. Structures for the complex alkoxides are discussed. Vapour pressures and vapour densities were measured for zirconium tetraethoxide and tetra*iso*propoxide and it is suggested that the vaporisation process is $[Zr(OR)_4]_n$ (liquid) $\longrightarrow$ $nZr(OR)_4$ (vapour), and that the energy of intermolecular attraction is *ca.* 18 kcals./mole. Entropies of vaporisation for the *n*-alkoxides of silicon and titanium increase with chain length, and this behaviour is discussed in terms of molecular "entanglement" in the liquid state.

IT has been established (Bradley, Mehrotra, and Wardlaw, *J.*, 1952, 2027, 4204, 5020 *) that the structure and volatility of the alkoxides of titanium and zirconium are governed by the configuration of the alkyl group. The purpose of the present research was to study the effect of chain length on the molecular complexity and volatility of the *n*-alkoxides and to discover the nature and strength of intermolecular forces in the complex molecules. In addition, it was expected that more information concerning the alkyl-group interaction postulated in Part III * would be forthcoming from the study of the *n*-alkoxides of silicon, titanium, and zirconium.

The following *n*-alkoxides of titanium and zirconium were prepared : $Ti(OC_nH_{2n+1})_4$

* Part III, *J.*, 1952, 5020.

where $n = 2$, 3, 4, 5, 6, 7, or 8, and $Zr(OC_nH_{2n+1})_4$ where $n = 2$, 3, 4, 5, 6, or 8. Except for the ethoxides these were prepared by alcohol interchange from the *iso*propoxides. Titanium tetraethoxide was prepared from the tetrachloride by the ammonia method (*loc. cit.*, p. 2027), and zirconium ethoxide was prepared by the method of Bradley, Halim, Sadek, and Wardlaw (*J.*, 1952, 2032) from pyridinium zirconium hexachloride. Zirconium *n*-hexyloxide could not be distilled without decomposition at 0·05 mm. and no attempt

TABLE 1.

	Titanium alkoxide			Zirconium alkoxide		
Alcohol	B. p./0·1 mm.	*M*	*X*	B. p./0·1 mm.	*M*	*X*
Ethanol	103°	556	2·4	180° *	980	3·6
Propanol	124	—	—	208	—	—
Butan-1-ol	142	—	—	243	1290	3·4
Pentan-1-ol	158	565	1·4	276	1428	3·2
Hexan-1-ol	176	—	—	>300	—	—
Heptan-1-ol	201	—	—	—	—	—
Octan-1-ol	214	781	1·4	—	2046	3·4

* Sublimed.

was made to distil zirconium *n*-octyloxide. Molecular weights (*M*) were determined on freshly distilled alkoxides in boiling benzene and the results, including molecular complexity (*X*) and boiling points, are presented in Table 1. This shows two outstanding features : (*a*) that molecular complexity in the zirconium alkoxides is much greater than in the titanium alkoxides and (*b*) that molecular complexity in both series is little affected by chain length. Whilst this work was in progress the results of Cullinane, Chard, Price, Millward, and Langlois (*J. Appl. Chem.*, 1951, **1**, 400) were reported. They found cryoscopically that molecular weights of titanium *n*-alkoxides (ethyl to *n*-hexyl) were approximately dimeric in benzene but that they depended on the concentration. Caughlan, Smith, Katz, Hodgson, and Crowe (*J. Amer. Chem. Soc.*, 1951, **73**, 5652), using the same method to determine the molecular weights of titanium tetraethoxide, tetra-*n*-propoxide, and tetra-*n*-butoxide, similarly found them to depend on concentration and to approach the trimeric state at high concentrations. It is interesting that our measurements in boiling benzene showed no significant variation of molecular weight of the titanium or zirconium compounds with concentration and that the molecular weight (in the titanium series) determined ebullioscopically is lower than that found cryoscopically. It appears that the molecular complexity of titanium *n*-alkoxides is a function of temperature. Neither titanium methoxide nor zirconium methoxide is soluble in suitable organic solvents and it was not possible to determine their molecular weights but this fact in conjunction with their very low volatilities suggests that they have complex structures.

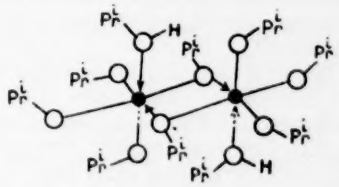
That molecular complexity is greater in zirconium alkoxides than in the corresponding titanium alkoxides can be explained as due either to stereochemical effects or to a difference in strength of the intermolecular binding. The stereochemical argument is very feasible in view of the greater atomic radius and maximum covalency of zirconium and evidence will be presented which suggests that the strength of intermolecular binding involving titanium and oxygen is comparable with that involving zirconium and oxygen.

Caughlan *et al.* (*loc. cit.*) suggested that each titanium atom in the trimeric alkoxides is surrounded octahedrally by oxygen atoms from alkoxide groups and that the trimeric unit comprises three octahedra bound by common faces. A similar arrangement seems reasonable for trimeric zirconium alkoxides but the molecular complexity in zirconium normal alkoxides is significantly greater than three. The fractional value suggests that a species of higher molecular complexity is present and a possible structure for a pentameric complex is shown in Fig. 1 in which octahedra share edges or faces. These structures involve zirconium with the co-ordination number 6 and the possibility that zirconium attains the co-ordination number 8 in these compounds cannot be ignored. However, the higher co-ordination number would lead to structures with a complexity much greater than three. Additional information concerning the nature of intermolecular bonding in the complex molecules has been obtained from molecular-weight determinations on zirconium ethoxide and zirconium *iso*propoxide in ethyl and *iso*propyl alcohol

respectively. Thus zirconium ethoxide, which has a complexity of 3·6 in benzene, has a value of 2·5 in ethyl alcohol, whilst zirconium *iso*propoxide is trimeric in benzene and dimeric in *iso*propyl alcohol. The complexity of the zirconium alkoxide is lower in the alcohol presumably because bonds of type $\begin{matrix}R\\H\end{matrix}\!\!>\!O\rightarrow Zr$ replace those of type $\begin{matrix}R\\Zr\end{matrix}\!\!>\!O\rightarrow Zr$. The dimeric *iso*propoxide may well have the structure shown in Fig. 2. This structure has the empirical formula $Zr(OPr^i)_4,Pr^iOH$ which was found for the crystalline complex *iso*propoxide.

FIG. 1.

FIG. 2.



R *groups omitted.* $[Zr(OR)_4]_3$. ● = Zr; ○ = *Oxygen.*

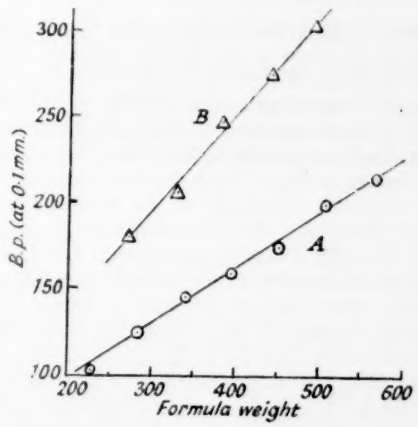


FIG. 3. *Normal alkoxides of* (A) *titanium, and* (B) *zirconium.*

The boiling points of the *n*-alkoxides of titanium and zirconium have been plotted against formula weights and the results are shown in Fig. 3. In both series there is a linear relation between boiling point and formula weight.

In Part I a linear relation between boiling point and molecular complexity was found for zirconium amyloxides and the possibility was envisaged that structure in the complex molecules might persist in the vapour state. Some preliminary vapour-pressure measurements have been made on zirconium tetraethoxide and tetra*iso*propoxide, and the results have given important information concerning the vaporisation process in these cases. The results conformed to the equation $\log p = a - b/T$ in the pressure range 2—10 mm. (see Table 2 where the symbols have their usual meaning; *loc. cit.*, p. 4204).

TABLE 2.

Alkoxide	$T_{5\cdot0}$	a	b	L_V	$\Delta S_{5\cdot0}$
$Zr(OEt)_4$	234·8	13·7	6600	30·2	59·4
$Zr(OPr^i)_4$	203·8	15·2	6895	31·5	66·0
$Zr(OBu^t)_4$	89·1	9·9	3330	15·2	42·0

Results for zirconium tetra-*tert.*-butoxide are given for comparison. The important factor which emerges is that the latent heats (L_V) and entropies of vaporisation (ΔS) are much greater for the complex alkoxides than for the monomeric zirconium *tert.*-butoxide. The

abnormally high entropies of vaporisation suggest that the vaporisation process involves a change from a liquid containing complex molecules to a monomeric vapour state, *viz.* :

$$\underset{\text{Liquid}}{[Zr(OR)_4]_n} \rightleftharpoons \underset{\text{Vapour}}{nZr(OR)_4}$$

That the alkoxides are monomeric in the vapour state has been confirmed by vapour-density determinations on zirconium ethoxide and *iso*propoxide. These facts have enabled us to make a preliminary assessment of the energy of intermolecular bonding in the complex molecules. From the approximately linear relation between boiling point and formula weight in the monomeric *tert.*-alkoxides (*loc. cit.*, p. 4204) the boiling points ($T_{mon.}$) of zirconium ethoxide and *iso*propoxide in the hypothetical " monomeric " state have been calculated.

The hypothetical " monomeric " latent heats ($L_{mon.}$) were then obtained by assuming that entropies of vaporisation in the " monomeric " state are the same as for zirconium *tert.*-butoxide. Thus, $L_{mon.} = T_{mon.}\Delta S = 42{\cdot}0T_{mon.}$. The " monomeric " latent heats are $Zr(OEt)_4$ 12·6, and $Zr(OPr^i)_4$ 13·8 kcal./mole; and these values seem reasonable compared with the experimental value 15·2 kcal./mole for zirconium *tert.*-butoxide. The energy of intermolecular bonding in the complex alkoxides is then given by $E = L_v - L_{mon.}$; and the values for E are $Zr(OEt)_4$ 17·6, and $Zr(OPr^i)_4$ 17·7 kcal./mole. If it is further assumed that each zirconium atom participates in two intermolecular bonds with oxygen in the liquid state, then the energy of the $\overset{Zr}{R}\!>\!O\rightarrow Zr$ bond is approximately 9 kcal. This is a relatively small value and suggests that the type of bonding may be electrostatic, $\overset{\delta+}{Zr}\cdots\overset{\delta-}{O}$, in nature rather than of the covalent type $\overset{-}{Zr}\text{–}\overset{+}{O}$. Brown, Taylor, and Sugishi's measurements (*J. Amer. Chem. Soc.*, **1951**, **73**, 2464) of the dissociation of the addition compounds of trimethylboron with aliphatic amines gave values of the order of 18 kcal. for the energy of the boron–nitrogen bond which is probably of the covalent type, whereas the hydrogen bond which is believed to be electrostatic has a bond energy of the order of 4·5 kcal. (Pauling, " The Nature of the Chemical Bond," Cornell Univ. Press, 1940).

In Part III it was suggested that the anomalous entropies of vaporisation of certain monomeric alkoxides of silicon and titanium were due to interaction of the alkyl groups and that this conception could be tested by studying the *n*-alkoxides of silicon and titanium. Cullinane *et al.* (*loc. cit.*) gave boiling points at various pressures for the titanium *n*-alkoxides $Ti(OC_nH_{2n+1})_4$ where $n = 2$, 3, 4, 5, and 6. Although their data do not conform very accurately to the relation $\log p = a - b/T$, we have made provisional calculations of latent heats and entropies of vaporisation from them. In addition the vapour pressures of *n*-butyl and *n*-hexyl orthosilicate have been measured whilst the data for the ethyl orthosilicate have been taken from Post (" Organic Silicon Compounds,"

TABLE 3.

Alkoxide	L_v	Trouton constant	Alkoxide	L_v	Trouton constant
$Si(OEt)_4$	11·25	25·7	$Ti(OEt)_4$	21·6	42·5
$Si(OBu^n)_4$	14·84	28·0	$Ti(OPr^n)_4$	15·7	29·1
$Si(OHex^n)_4$	21·78	33·5	$Ti(OBu^n)_4$	20·1	35·6
			$Ti(OAm^n)_4$	23·1	39·4
			$Ti(OHex^n)_4$	24·6	40·5

Reinhold Publ. Corp., New York, 1949). The latent heats and Trouton constants (Table 3) present strong evidence that alkyl-group interaction occurs in the *n*-alkoxides of silicon and titanium. In the case of ethyl orthosilicate the intermolecular attraction involving silicon and oxygen must be relatively small and should decrease steadily with increase in size of alkyl group. However, it is found that the entropies of vaporisation increase with alkyl chain length. This effect is partly due to the increase in Trouton's constant with decrease in vapour concentration at 760 mm. at the higher boiling points (cf. Hildebrand, *J. Amer. Chem. Soc.*, **1915**, **37**, 970). Accordingly, the entropies of vaporisation (cal./deg./mole), corrected to the same vapour concentration, were calculated and found to be $Si(OEt)_4$ 25·7, $Si(OBu^n)_4$ 27·1 and $Si(OC_6H_{13-n})_4$ 31·7. We suggest that this increase

in entropy of vaporisation with increase in chain length is due to molecular " entanglement " in the liquid state. A molecule $M(OC_nH_{2n+1})_4$ can be considered as equivalent to two chains of $(2n + 3)$ atoms fused at the central atom M and the possibility of entanglement of such tenuous structures is evident. A molecule in the liquid will require special orientation in order to be disentangled before vaporisation, and this increases the entropy of vaporisation. This theory enables us to interpret the surprising order of Trouton constants for the titanium normal alkoxides (Table 3). First, the high value for the ethoxide is attributed to the presence of complex molecules involving $\begin{matrix}Ti\\R\end{matrix}\!>\!O\rightarrow Ti$ bonds and it is clear that the vaporisation process in $Ti(OEt)_4$ resembles that of the complex zirconium alkoxides. Thus $\Delta S_{5\cdot0}$ is 52·6 cal./deg./mole for $Ti(OEt)_4$ [cf. 59·4 for $Zr(OEt)_4$] and E is 10 kcal./mole [cf. 17·6 for $Zr(OEt)_4$]. If allowance is made for the greater shielding of titanium in $Ti(OEt)_4$ (complexity = 2·4) than of zirconium in $Zr(OEt)_4$ (complexity = 3·6) it seems possible that the energy of $\begin{matrix}M\\R\end{matrix}\!>\!O\rightarrow M$ bonds is approximately the same for M = Ti or Zr. The greater shielding power of propoxide groups explains the decrease in molecular complexity and Trouton constant in passing from the ethoxide to the *n*- or *iso*-propoxide of titanium. Further increase in length of alkyl group leads to an increase in Trouton's constant, which can be ascribed to the predominance of the " entanglement " process.

Although the alkyl-group interaction has provisionally been interpreted as due to molecular " entanglement " in the liquid an alternative explanation in terms of restricted rotation of alkoxide groups is possible. This would require free rotation in the vapour and restricted rotation in the liquid, whilst the amount of rotation in the liquid should decrease with increase in alkyl chain length. Unfortunately, the published data on the dipole moments of these compounds are inconsistent and more accurate measurements are required before a decision can be made.

Experimental

The apparatus used and the methods of analysis and determination of b. p. of the alkoxides were as reported previously (*loc. cit.*).

Preparation of n-*Alkoxides of Titanium and Zirconium.*—The preparations of titanium ethoxide and zirconium ethoxide have been reported (Bradley, Hancock, and Wardlaw, *J.*, 1952, 2773; Bradley, Halim, Sadek, and Wardlaw, *J.*, 1952, 2032). The higher *n*-alkoxides were prepared by alcohol-interchange involving the *iso*propoxides by the methods previously described (*J.*, 1952, 2027, 4204, 5020). The results are summarised in the annexed Table.

R	$M(OPr^i)$ taken (g.)	ROH taken (g.)	C_6H_6 (c.c.)	Yield (g.)	B. p./mm.	Found, M (%)	Reqd., M (%)
Titanium compounds.[a]							
n-Propyl...	6·7	8·0	60	6·3	138°/0·5, 124°/0·1	16·87	16·85
n-Butyl ...	5·7	7·2	60	6·3	160°/0·8, 142°/0·1	14·10	14·07
n-Amyl ...	6·4	9·1	60	8·4	175°/0·8, 158°/0·1	12·16	12·09
n-Hexyl ...	6·1	10·3	65	9·3	193°/0·8, 176°/0·1	10·53	10·58
n-Heptyl	3·9	9·5	50	6·1	213°/0·4, 201°/0·1	9·42 †	9·42
n-Octyl ...	14·3	33·7	80	25·3	228°/0·5, 214°/0·1	8·52	8·48
Zirconium compounds.							
n-Propyl...	8·0	7·3	70	6·3[b]	198°/0·03, 208°/0·1	27·85	27·85
n-Butyl ...	8·5	8·0	70	7·6[c]	253°/0·3, 243°/0·1	23·8	23·8
n-Amyl ...	5·7	10·7	60	6·2[b]	256°/0·01, 276°/0·1	20·8	20·75
n-Hexyl ...	9·7	20·4	80	12·0[d]	310—320°/0·5—0·6[e]	18·25	18·4
n-Heptyl	4·2	7·0	50	5·9[b]	Dried at 170°/0·2 mm.	16·6 †	16·5
n-Octyl ...	6·3	10·7	40	9·9[b]	,, 180°/0·2 mm.	15·1 †	15·0

[a] Mobile liquid. [b] Highly viscous liquid. [c] Solid. [d] Liquid slowly set to white solid. [e] Decomposition.

† The following carbon and hydrogen analyses were determined:

$Ti(OC_7H_{15})_4$:	Found:	C, 66·3;	H, 11·9.	Reqd.: C, 66·1;	H, 11·9%.
$Zr(OC_7H_{15})_4$		60·8	11·1	60·9	11·0
$Zr(OC_8H_{17})_4$		62·1	11·2	63·2	11·3

n-*Butyl Orthosilicate*.—Silicon tetrachloride (45 g.) was added dropwise to *n*-butyl alcohol (80 g.), and the liquid product aspirated for 2 hr. to remove hydrogen chloride. Volatile constituents were completely removed under reduced pressure, and the *n*-butyl orthosilicate obtained by distillation (b. p. 95—100°/0·1—0·2 mm.) as a colourless mobile liquid (75 g.) [Found : Si, 8·7. Calc. for $Si(OC_4H_9)_4$: Si, 8·8%], b. p. 115°/1·5, 118°/2·2, 121°/2·6, 127°/4·0, 129°/4·5, 134°/5·5, 137°/6·3, 140°/7·7, 143°/8·6, 149°/11·0, 161°/21, 188°/68, 194°/90, 202°/110, 213°/156, 235°/305, 268°/752 mm. $\text{Log}_{10}P$ (mm.) = 8·88 − 3246/T; L_v = 14·84 kcal./mole.

n-*Hexyl Orthosilicate*.—From the reaction involving silicon tetrachloride (45 g.) and *n*-hexyl alcohol (115 g.), *n*-hexyl orthosilicate (83·2 g.; b. p. 170°/0·8 mm.) was isolated as described for the *n*-butyl ester [Found : Si, 6·45. Calc. for $Si(OC_6H_{13})_4$: Si, 6·5%], b. p. 181°/1·75, 187°/2·5, 190°/2·9, 195·5°/4·5, 209°/8·0, 212°/9·0, 216°/11·0, 228°/18·5, 232°/21·0, 265°/76, 271°/80, 300°/250 mm. $\text{Log}_{10}P$ (mm.) = 10·33 − 4545/T; L_v = 21·8 kcal./mole.

Molecular Weights.—Determinations in benzene were carried out ebullioscopically in the apparatus previously described. Determinations in ethyl alcohol or *iso*propyl alcohol were made in a new apparatus by a method, to be described later, which involved weighing the solvent. In all cases the plot of Δt against concentration was linear within experimental error. Results are summarised in the annexed Table.

Vapour Densities.—Vapour density was evaluated by determining the amount of zirconium remaining in a flask (500 c.c.) after removal of the alkoxide at known temperature (*ca.* 50° above the b. p.) and pressure (*ca.* 10 mm.). Although these preliminary results are not accurate they nevertheless suggest that zirconium ethoxide and *iso*propoxide are probably monomeric in the vapour. Results were : $Zr(OEt)_4$: Found : *M*, 288. Calc. : *M*, 271. $Zr(OPr^i)_4$, Found : *M*, 384. Calc. : *M*, 327.

Alkoxide	Range of wts. (g.)	Solvent (c.c.)	*M*, found	*M*, calc.
$Ti(OC_2H_5)_4$	0·128—0·794	35·6 [a]	556	228·1
$Zr(OC_2H_5)_4$	0·090—0·907	35·3 [a]	980	271·5
$Zr(OC_4H_9)_4$	0·241—0·811	35·8 [a]	1290	383·7
$Ti(OC_5H_{11})_4$	0·167—1·116	36·2 [a]	565	396·5
$Zr(OC_5H_{11})_4$	0·567—1·785	35·7 [a]	1428	439·8
$Ti(OC_8H_{17})_4$	0·550—1·836	34·0 [a]	781	564·8
$Zr(OC_8H_{17})_4$	0·176—1·825	35·8 [a]	2046	608·1
$Zr(OC_2H_5)_4$	0·146—1·779	14·70 [b]	678	271·5
$Zr(OPr^i)_4,Pr^iOH$	0·090—0·734	18·21 [c]	732	387·6

[a] Benzene. [b] Ethyl alcohol (g.). [c] *iso*Propyl alcohol (g.).

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413. *Protozoal Polysaccharides. Structure of a Polysaccharide produced by* Cycloposthium.

By G. Forsyth, E. L. Hirst, and A. E. Oxford.

The ciliated protozoon *Cycloposthium* found in the colon and cæcum of a horse synthesises as reserve material a polysaccharide of high molecular weight, which contains only glucose residues. Examination of this material by the methylation method and by the periodate oxidation procedure has shown that its highly branched molecular structure is closely similar to that of amylopectin. The unit chains contain on an average 23 α-1 : 4-linked glucopyranose residues and are joined by $C_{(1)}$–$C_{(6)}$ linkages.

It has been shown that certain intestinal protozoa synthesise glucose-containing polysaccharides which are stored intracellularly as food reserve materials (Oxford, *J. Gen. Microbiol.*, 1951, **5**, 83; Heald and Oxford, *Biochem. J.*, 1953, **53**, 506). These materials are stained reddish-brown by iodine, and a chemical examination of a sample produced by a free-living protozoan *Tetrahymena piriformis* led to the conclusion that it was a typical animal glycogen of molecular weight about 10^7, possessing an average unit chain length of 13

glucose residues (Ryley, *Biochem. J.*, 1951, **49**, 577; Manners and Ryley, *ibid.*, 1952, **52**, 480). It is now clear, however, that considerable differences in structure may occur between the glucose-containing polysaccharides synthesised by protozoa. The present paper is concerned with a study of a polysaccharide isolated from the large protozoon *Cycloposthium* (Class, Ciliophora; Sub-Class Ciliata) which was found in large numbers in the colon and cæcum of a horse (see Adam, *Parasitology*, 1951, **41**, 301, concerning the distribution of ciliate protozoa in this animal's large intestine). The protozoa, separated from the liquid contents of the colon and cæcum, were so rich in polysaccharide as to be stained almost black by iodine. This intracellular carbohydrate occurs in the form of coherent masses which are structural features characteristic of the cell. After extraction by chloral hydrate it was obtained as a white powder in a yield of 50% by weight of the dried protozoa. By this method of extraction the morphologically discrete character of the polysaccharide cannot be preserved but little or no alteration of the main chemical structure is brought about. The material gave a red-purple colour with iodine and had a specific rotation ($[\alpha]_D$) of $+190°$ in 30% aqueous perchloric acid and $+154°$ in N-sodium hydroxide, the values being similar to those of amylopectin. The low " blue value " (Hassid and McCready, *J. Amer. Chem. Soc.*, 1943, **65**, 1154; Haworth, Peat, Bourne, and Macey, *J.*, 1948, 924) indicated that material of amylose type was present in negligible amount. Hydrolysis with acid gave glucose as the only sugar. The amount of formic acid produced when the polysaccharide was oxidised by potassium periodate corresponded to the presence of one non-reducing terminal glucose residue for every 23 glucose units in the molecule. The reaction proceeded without complications and followed exactly the course observed with amylopectin (Brown, Halsall, Hirst, and Jones, *J.*, 1948, 27). After oxidation by periodate the residual polysaccharide was subjected to acid hydrolysis and the products were examined chromatographically. Only a trace of glucose was present and it is therefore clear that the proportion of glucose residues not accessible to attack by periodate must be very small, certainly less than 1%. There can be few, if any, glycosidic linkages involving either $C_{(2)}$ or $C_{(3)}$ of any of the glucose residues, and the great majority of the inter-unit bonds must be of the 1 : 6-type.

Methylation of the polysaccharide was carried out in nitrogen by methyl sulphate and sodium hydroxide. The trimethyl derivative had properties very similar to those of methylated amylopectin. It showed a relatively high specific viscosity in *m*-cresol, corresponding to a molecular weight of about 200,000 when the constant given by Hirst and Young (*J.*, 1939, 1471) was used. This trimethyl derivative was heated with methanolic hydrogen chloride, and the methylated methylglucosides so obtained were hydrolysed with aqueous hydrochloric acid. The mixture of reducing sugars was examined chromatographically both on paper strips and on a column of powdered cellulose. The substances present were 2 : 3 : 4 : 6-tetramethyl D-glucose, 2 : 3 : 6-trimethyl D-glucose, 2 : 3-dimethyl D-glucose, and a mixture of 2 : 6- and 3 : 6-dimethyl glucose which probably owed their origin to incomplete methylation of the polysaccharide or to some slight demethylation during hydrolysis. Only traces of monomethyl glucose and free glucose were found.

The yield of tetramethyl glucose corresponded to the presence of one non-reducing terminal glucose residue for every 23 glucose units in the molecule. This value is identical with that found by the periodic acid method and it follows that the polysaccharide from *Cycloposthium* has an average unit chain length of 23 glucose residues. In this respect and in its high specific viscosity in solution it resembles amylopectin much more closely than it does glycogen. It clearly possesses a highly branched structure of the amylopectin type but in the absence of detailed enzymic studies on the lines employed by Cori and by Peat for glycogen and starch no estimate of the extent of multiple branching can yet be made. In conclusion it may be remarked that in the present state of knowledge it would be preferable not to designate polysaccharides of this type as glycogen or amylopectin solely by reason of the unit chain length present in their molecules. Amylopectins generally differ from glycogen in having high specific viscosities. This, as has been indicated previously (Halsall, Hirst, Hough, and Jones, *J.*, 1949, 3203), may imply some fundamental variation in molecular structure and must be taken into account in any detailed formulation of the arrangement of the unit chains. In the particular case now investigated the high viscosity would point to a structure resembling that of amylopectin, despite the fact

that the biological relations of the protozoa would have rendered a glycogen type of structure more probable for the reserve material.

Experimental

Isolation of a Polysaccharide from the Colon and Cæcum of a Horse.—The contents (*ca.* 25 l.) of the ventral colon and the cæcum of a freshly slaughtered horse were filtered through three layers of muslin, the brown filtrate being set aside until the solid material had settled. The coarse material retained on the muslin was suspended in distilled water, refiltered, and then discarded. After the combined filtrates had been kept for 2 hr. the supernatant liquor was decanted, leaving on the bottom of each container a fine white residue. These residues were combined, washed with distilled water, and allowed to settle, and the supernatant liquor was decanted. After three such treatments, the moist solid was found, under the microscope, to consist almost entirely of the protozoon *Cycloposthium*. Each individual protozoon was stained dark brown or black by iodine. As far as could be observed, such impurities as other protozoa, parasitic worms, or their eggs were absent. After centrifugation to remove most of the adherent water the product was dried over phosphoric oxide in a desiccator at room temperature.

This material (8·0 g.) was extracted with chloral hydrate as described by Meyer and Bernfield (*Helv. Chim. Acta*, 1940, **23**, 875). The product (3·8 g.) was obtained as a colourless, easily powdered polysaccharide, the residue (3·9 g.) consisting of coarse, dark brown, fibrous material which was not investigated further.

Properties of the Polysaccharide.—A suspension of the polysaccharide in water gave a purple colour with iodine. In boiling 4% sulphuric acid (200 parts) the substance (1 part) yielded 86% of the theoretical amount of glucose (quantitative chromatographic determination). No sugar other than glucose was detected. The material had $[\alpha]_D^{14}$ +154° (*c*, 1·0 in N-NaOH), +190° (*c*, 0·4 in 4·8N-$HClO_4$). The blue value, determined in the standard manner (*locc. cit.*), was 0·10.

Oxidation by Periodate.—The sample (0·293 g.) was treated with sodium metaperiodate and potassium chloride (Brown, Halsall, Hirst, and Jones, *loc. cit.*), the acid titre after 150 hr. corresponding to 0·041 mole of formic acid from 162 g. of polysaccharide, *i.e.*, 1 mol. per 24 glucose residues. A duplicate experiment yielded one mol. of formic acid per 23 glucose units.

After completion of the formic acid determinations, the solutions were combined, excess of periodate being destroyed by the addition of excess of ethylene glycol (overnight shaking). The insoluble oxidised polysaccharide was filtered off, washed with water till free from iodate, and then dried by washing with ethanol and ether. This material was hydrolysed with sulphuric acid (10 ml.; 0·5N) at 95° for 8 hr. After neutralisation with barium carbonate, followed by filtration and evaporation to dryness, the residue was examined in the normal way by paper chromatography. No glucose or other reducing sugar was observed.

Methylation of the Polysaccharide.—The sample (1·8 g.) was methylated under the conditions used by Hirst, Jones, and Roudier (*J.*, 1948, 1779), 18 additions of reagents being made. The product (1·24 g.) was purified by precipitation from chloroform with light petroleum (b. p. 100—120°). The product had $[\alpha]_D^{17}$ +207° (*c*, 1·0 in $CHCl_3$), $\gamma_{sp.}/c$ 1·27 (*c*, 0·4 in *m*-cresol), corresponding to an apparent M = 175,000 (Found : OMe, 43·1%).

Hydrolysis of the Methylated Polysaccharide.—(*a*) The material (50 mg.) was hydrolysed in a sealed tube by the method of Hough, Hirst, and Jones (*J.*, 1949, 928). Analyses by paper chromatography with butanol–light petroleum saturated with water as mobile phase revealed the 2 : 3 : 4 : 6-tetramethyl glucose R_G 1·0 (5·3%), 2 : 3 : 6-trimethyl glucose R_G 0·81 (84%), and dimethyl glucoses R_G 0·63, 0·54 (12%). Traces of monomethyl glucose and of glucose were also observed. These results indicate the presence of one non-reducing terminal group per 21 ± 1 glucose residues.

(*b*) The material (0·88 g.) was hydrolysed by boiling methanolic hydrogen chloride (40 ml.; 1%) for 9 hr. After neutralisation with silver carbonate, treatment with hydrogen sulphide, etc., and concentration, the resulting syrup was boiled with hydrochloric acid (40 ml.; 2%) for 8 hr. After neutralisation with silver carbonate, and concentration, a syrup (0·88 g.) was obtained which partly crystallised. This mixture of methylated glucoses was separated on a column (50 × 3 cm.) of powdered cellulose (Whatman No. 1 ashless filter tablets) (Hough, Jones, and Wadman, *J.*, 1950, 1702; Chanda, Hirst, Jones, and Percival, *J.*, 1950, 1289). By elution with 2 : 3 *n*-butanol–light petroleum (b. p. 100—120°) saturated with water, four fractions were isolated, *viz.*, (1) 0·105, (2) 0·452, (3) 0·050, and (4) 0·020 g. By elution of the

column with water, a further fraction (0·008 g.) was obtained. Paper chromatography indicated that the last fraction, which was not further investigated, contained monomethyl glucose and glucose. The total recovery of sugars was 91%.

Fraction (1). Paper chromatography indicated the presence of a single substance (R_G 1·0) which corresponded to tetramethyl glucose. A small portion was hydrolysed with boiling 4% sulphuric acid, and after neutralisation was re-examined by paper chromatography. The presence of two substances was then indicated corresponding to 2 : 3 : 4 : 6-tetramethyl glucose and 2 : 3 : 6-trimethyl glucose (R_G 0·81). Hypoiodite oxidation indicated that the fraction (1) contained 25% of tetramethyl glucose. Fraction (1) was therefore rehydrolysed with hydrochloric acid (10 ml.; 1%) for 7 hr. The hydrolysate was separated on a fresh cellulose column (50 × 1·5 cm.), giving fractions (1*a*) 0·027 and (1*b*) 0·066 g. (93% recovery). Fraction (1*a*) partly crystallised and was found by hypoiodite oxidation to be 98% pure. After crystallisation twice from light petroleum (b. p. 40—60°) it had m. p. 84—85° (not depressed on admixture with authentic 2 : 3 : 4 : 6-tetramethyl D-glucopyranose), $[\alpha]_D^{14}$ + 84° (*c*, 0·5 in H_2O) (Found : OMe, 52·1. Calc. for $C_{10}H_{20}O_6$, 52·5%). From these results it followed that the polysaccharide contained one non-reducing terminal group per 22 ± 2 glucose units.

Fraction (1*b*) did not crystallise. Paper chromatography indicated the presence of a single substance (R_G 0·81) corresponding to 2 : 3 : 6-trimethyl glucose. It had $[\alpha]_D^{14}$ + 69° (*c*, 1·0 in H_2O), +67° (initial), dropping to −38° after 8 hr. in 2% methanolic hydrogen chloride (*c*, 1·0) (Found : OMe, 40·9. Calc. for $C_9H_{18}O_6$: OMe, 41·9%).

Fraction (2), which partly crystallised, was recrystallised twice from butyl acetate, and had m. p. 117°, alone or admixed with authentic 2 : 3 : 6-trimethyl D-glucose. The crystalline material had $[\alpha]_D^{16}$ +87° (initial), +68° (const.) (*c*, 1·0 in H_2O), and $[\alpha]_D^{14}$ +67° (initial), −38° (8 hr.) (*c*, 1·0 in 2% methanolic hydrogen chloride) (Found : OMe, 41·4%).

Fraction (3) was obtained as a syrup which failed to crystallise during several weeks in the cold. The R_G value (0·62) was identical with that of 2 : 3-dimethyl D-glucose. The material had $[\alpha]_D^{15}$ +106° (initial), +65° (final) (*c*, 1·0 in H_2O) (Found : OMe, 29·3. Calc. for $C_8H_{16}O_6$: OMe, 29·7%).

Fraction (4) was a syrup which failed to crystallise during several weeks in the cold. Paper chromatography indicated the presence of 2 : 6- or 3 : 6-dimethyl D-glucose (R_G 0·54) or a mixture of the two, contaminated with traces of 2 : 3-dimethyl D-glucose. It had $[\alpha]_D^{13}$ +83° (initial), +62° (final) (*c*, 1·0 in H_2O), +62° (initial), −12° (final, 12 hr.) (*c*, 0·7 in 2% methanolic hydrogen chloride) (Found : OMe, 29·1%). The fraction was converted into the methyl glucosides and treated with sodium metaperiodate by Bell's method (*J.*, 1948, 992). The uptake of sodium metaperiodate indicated that the fraction contained 70% of 2 : 6-dimethyl D-glucose.

The authors gratefully record the interest taken by the late Dr. E. G. V. Percival in the early stages of this work. They thank the Department of Scientific and Industrial Research for a maintenance allowance to one of them (G. F.), and the Distillers Company Ltd. and Imperial Chemical Industries Limited for grants. They are grateful to the officers of the Royal Zoological Society of Scotland for providing facilities, to Dr. I. W. Parnell of the Zoological Department of the University of Edinburgh for assistance in the collection of the material and in its transport to the University, and to Dr. F. Alexander, M.R.C.V.S., for making the arrangements.

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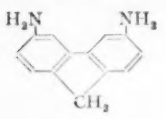
414. 3 : 6-*Disubstituted Fluorenes. Part I. The Attempted Introduction of a* 6 : 6′-*Methylene Bridge Directly into* 3 : 3′-*Diaminodiphenyl and Some of its Derivatives.*

By A. Barker and C. C. Barker.

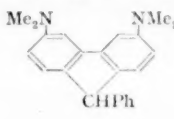
Earlier claims to have prepared 3 : 6-bisdimethylamino-9-phenylfluorene from 3 : 3′-bisdimethylaminodiphenyl and benzylidene chloride, and the lactone of *o*-3 : 6 : 9-trihydroxy-9-fluorenylbenzoic acid from 3 : 3′-dihydroxydiphenyl and phthalic anhydride, are refuted.

It is also shown that fluorene derivatives are not formed by condensing formaldehyde with 3 : 3′-diaminodiphenyl, 3 : 3′-bisdimethylaminodiphenyl, or 3 : 3′-bisdimethylamino-4 : 4′-dimethyldiphenyl. Formaldehyde appears to attack such amines only at a vacant 4-position.

Present knowledge of 3 : 6-disubstituted fluorenes is limited to 3 : 6-dibromofluorene, obtained from 3 : 6-dibromophenanthraquinone by Courtot and Kronstein (*Chim. et Ind.* [special number], 1941, **45**, 72), and 3 : 6-dimethylfluorene, obtained from 2-amino-4 : 4′-dimethylbenzophenone by Chardonnens and Wurmli (*Helv. Chim. Acta*, 1946, **29**, 922). The unknown 3 : 6-diaminofluorene (I) is thus of interest, both as a precursor, and as the parent substance of the unknown fluorene analogue of Michler's hydrol. The absorption spectrum of the colour salt of the latter, together with those of related dyes, might yield information about the configuration of the fluorene molecule.



(I)



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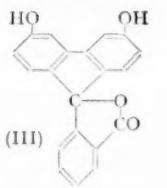

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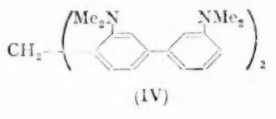

(IV)

The literature indicates that derivatives of this amine can be synthesised from the corresponding diaminodiphenyl and formaldehyde. Thus, Adam (*Compt. rend.*, 1886, **103**, 207) obtained fluorene and bis-4-diphenylylmethane, from methylene dichloride and diphenyl in the presence of aluminium chloride, although Meyer and Wesche (*Ber.*, 1917, **50**, 442) failed to repeat the preparation, and Weiler (*Ber.*, 1874, **7**, 1188) obtained only bis-4-diphenylylmethane from diphenyl and dimethoxymethane in the presence of concentrated sulphuric acid. Dutt (*J.*, 1926, 1171) claims to have prepared 3 : 6-bisdimethylamino-9-phenylfluorene (II), from benzylidene chloride and 3 : 3′-bisdimethylaminodiphenyl, and also the lactone (III) of *o*-3 : 6 : 9-trihydroxy-9-fluorenylbenzoic acid, from phthalic anhydride and 3 : 3′-dihydroxydiphenyl, both condensations being effected with aluminium chloride.

Products (II) and (III) are analogues of the leuco-base of malachite green and phenolphthalein, respectively, and their formation suggests the possibility of introducing a 6 : 6′-methylene bridge into diphenyl when powerful *para*-directing groups occupy the 3 : 3′-positions. Emde (*Chem. Zentr.*, 1915, II, 278), however, failed to obtain 3 : 6-diaminofluorene from 3 : 3′-diaminodiphenyl and formaldehyde, and attempts by the present authors confirmed that none was formed. This result was not regarded as decisive, since the action of formaldehyde on primary aromatic amines is often complex, and the condensation of formaldehyde with the tertiary base 3 : 3′-bisdimethylaminodiphenyl was therefore examined.

Dutt (*loc. cit.*) claimed to have prepared 3 : 3′-bisdimethylaminodiphenyl, m. p. 126—128°, by the methylation of 3 : 3′-diaminodiphenyl with methyl sulphate. In the present work, 3 : 3′-diaminodiphenyl dihydrobromide was methylated with methyl alcohol at 147°, and, after extensive purification, 3 : 3′-bisdimethylaminodiphenyl, m. p. 34·5°, was isolated and characterised. The same material was obtained by heating *m*-bromo-*NN*-

dimethylaniline with palladised calcium carbonate, hydrazine hydrate, and alcoholic potassium hydroxide. Considerable doubt is therefore thrown on the authenticity of Dutt's material. Moreover, condensation of authentic 3 : 3′-bisdimethylaminodiphenyl with benzylidene chloride, as described by Dutt, gave non-crystalline products which yielded no colour when oxidised in acid solution with lead peroxide—contrary to Dutt's claim to have prepared 3 : 6-bisdimethylamino-9-phenylfluorene and to have oxidised it to a coloured carbinol.

Attempts to repeat Dutt's preparation of (III) were equally unsuccessful, and it would appear that his claim, to have prepared these two compounds and to have measured the absorption maxima of their colour salts, is invalid.

The condensation of 3 : 3′-bisdimethylaminodiphenyl dihydrochloride and aqueous formaldehyde, in equimolecular amounts, gave no 3 : 6-bisdimethylaminofluorene. When the amount of formaldehyde was halved, the 3 : 3′-bisdimethylaminodiphenyl reacted completely to form a crystalline base, $C_{33}H_{40}N_2$, which is believed to be di-(3 : 3′-bisdimethylamino-4-diphenylyl)methane (IV). From this it would appear that a successful fluorene synthesis might be achieved when the reactive 4 : 4′-positions in the starting amine are occupied. Accordingly, 3 : 3′-bisdimethylamino-4 : 4′-dimethyldiphenyl was treated with formaldehyde, but the amine was recovered unchanged. This can only be attributed to steric hindrance at the 6 : 6′-positions, since *o*-dimethylaminotoluene condenses almost quantitatively with formaldehyde to give 4 : 4′-bisdimethylamino-3 : 3′-dimethyldiphenylmethane. This supports the structure (IV) for the base $C_{33}H_{40}N_4$, and indicates that a successful synthesis of 3 : 6-disubstituted fluorenes by the attempted route is unlikely.

Experimental

3 : 3′-*Bisdimethylaminodiphenyl.*—(*a*) 3 : 3′-diaminodiphenyl dihydrobromide (7·37 g.) and methyl alcohol (3·60 c.c.) were heated in a sealed tube for 11 hr. at 147° ± 2°. The product was made alkaline with dilute sodium hydroxide and extracted with ether. The dried extract (Na_2SO_4) was evaporated and the residue refluxed for 15 min. with acetic anhydride (15 c.c.) which was then removed at reduced pressure. The residue was dissolved in ether, and the filtered solution was washed with dilute sodium hydroxide and dried, the solvent removed, and the residue slowly distilled at 170° (bath-temp.)/10^{-3} mm. Two fractions, (i) (1·98 g.) and (ii) (0·65 g.), were collected. A solution of the partially solid (i) in benzene was adsorbed on activated alumina (1·4 × 15 cm.); elution in benzene (150 c.c.) gave 3 : 3′-*bisdimethylaminodiphenyl* (1·5 g.), m. p. 34·5° (Found : C, 78·9; H, 8·3; N, 12·0. $C_{16}H_{20}N_2$ requires C, 79·9; H, 8·3; N, 11·7%). The *dimethiodide* formed needles, m. p. 262—263° (decomp.), from aqueous alcohol (Found : C, 41·4; H, 4·8; N, 5·4; I, 47·8. $C_{16}H_{20}N_2.2CH_3I$ requires C, 41·2; H, 5·0; N, 5·3; I, 48·4%), and the *dipicrate*, micro-crystals, m. p. 202—203° (decomp.), from acetic acid (Found : N, 15·8. $C_{16}H_{20}N_2.2C_6H_3O_7N_3$ requires N, 16·0%).

(*b*) A mixture of *m*-bromo-*NN*-dimethylaniline (30·0 g.), methyl alcoholic potassium hydroxide (300 c.c.; 5% w/v), hydrazine hydrate (50% aqueous solution; 7·5 c.c.), and palladised calcium carbonate (15 g.; 0·5% of Pd) was heated in a steel autoclave at 135—140° for 90 min. (255 lb./in.²). The bulk of the alcohol was removed, giving a sludge which was extracted with hot benzene. After drying of the solution (Na_2SO_4) and removal of the solvent, a viscous oil was obtained which gave a semisolid fraction (6·0 g.), b. p. 195°/2 mm. Similar fractions from three experiments were combined (16·6 g.) and slowly distilled at 165—180° (bath-temp.)/10^{-3} mm., giving three fractions : (i) 1·89 g., $n_D^{12·5}$ 1·6335; (ii) 13·0 g., $n_D^{12·5}$ 1·6440; and (iii) 1·35 g., $n_D^{12·5}$ 1·6460. The middle fraction was purified by chromatography in benzene on activated alumina, 3 : 3′-bisdimethylaminodiphenyl, m. p. 33—34°, appearing in the fore-runnings. The m. p. was not depressed on admixture of the material with that from (*a*).

The Reaction of Formaldehyde with 3 : 3′-*Bisdimethylaminodiphenyl.*—3 : 3′-Bisdimethylaminodiphenyl dihydrochloride (1·76 g.; prepared by passing dry hydrogen chloride into a solution of the base in methyl alcohol and adding ether) was heated in a sealed tube with water (4·0 c.c.) and formalin (39·1% w/v; 0·215 c.c.) at 55° for 12 hr. and then at 95° for 30 hr. Basification of the solution yielded a white solid (1·4 g.), m. p. 60—70°, which gave a negligible amount of sublimate at 180°/10^{-3} mm. and therefore contained no 3 : 6-bisdimethylaminofluorene. This material was purified on alumina by using benzene as eluant. The fore-runnings yielded a syrup which solidified on addition of ethyl alcohol, giving *di*-(3 : 3′-*bisdimethylamino*-4-

diphenylyl)methane, m. p. 137—137·5° (from ethyl alcohol) [Found: C, 80·1; H, 8·0; N, 11·4%; *M* (micro-Rast), 495. $C_{33}H_{40}N_4$ requires C, 80·4; H, 8·2; N, 11·4%; *M*, 492].

3 : 3′-*Diamino*-4 : 4′-*dimethyldiphenyl*.—4 : 4′-Dimethyl-3 : 3′-dinitrodiphenyl, m. p. 178·5—179·5° (Adams and Patterson, *J. Amer. Chem. Soc.*, 1935, **57**, 762) was purified by sublimation at 155°/10^{-4} mm., followed by crystallisation from acetic acid. Dennett and Turner (*J.*, 1926, 480) give m. p. 175—176°. This nitro-compound (29 g.), iron pin dust (50 g.), concentrated hydrochloric acid (5·0 c.c.), and ethyl alcohol (85%; 500 c.c.) were vigorously stirred and refluxed for 40 hr. Sodium carbonate (5·0 g.) was added, refluxing continued for 30 minutes, and the iron sludge then removed. The liquors were concentrated to 200 c.c., concentrated hydrochloric acid (50 c.c.) was added, and the precipitated amine hydrochloride removed, washed with benzene, and basified with dilute sodium hydroxide. Sublimation of the resulting amine at 180°/10^{-3} mm., followed by crystallisation from aqueous alcohol, gave 3 : 3′-*diamino*-4 : 4′-*dimethyldiphenyl* (18·0 g.), m. p. 121° (Found: C, 79·2; H, 7·5; N, 13·2. $C_{14}H_{16}N_2$ requires C, 79·3; H, 7·5; N, 13·2%).

3 : 3′-*Bisdimethylamino*-4 : 4′-*dimethyldiphenyl*.—Trimethyl phosphate (2·5 c.c.) was added dropwise to 3 : 3′-diamino-4 : 4′-dimethyldiphenyl (2·0 g.) at 170°, and the temperature was raised to 195—200° for 1 hr. The product was refluxed for 1 hr. with aqueous sodium hydroxide (16% w/v; 30 c.c.), diluted with water, and extracted with ether. Evaporation of the dried extract gave a product, which, after being refluxed with acetic anhydride (6·0 c.c.) for 1 hr. and then freed from the acetic anhydride, was dissolved in dilute hydrochloric acid, the impurities extracted with benzene, and the aqueous layer basified. The precipitated solid (2·15 g.; m. p. 63—66°) was purified by chromatography on activated alumina, light petroleum (b. p. 60—80°) being used as eluant. The fore-runnings gave 3 : 3′-*bisdimethylamino*-4 : 4′-*dimethyldiphenyl* (1·8 g.), m. p. 67·5—68·5° (from light petroleum followed by methyl alcohol) (Found: C, 80·1; H, 9·0; N, 10·5. $C_{18}H_{24}N_2$ requires C, 80·6; H, 9·0; N, 10·4%).

Grateful acknowledgment is made to Distillers Co. Ltd. and to Imperial Chemical Industries Limited for grants. One of us (A. B.) thanks the University College of Hull for a Research Studentship, and the Lancashire County Council for personal grants.

University College, Hull. [*Received, April 1st*, 1953.]

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415. cyclo*Octatetraene Derivatives. Part I. Dimers of* cyclo*Octatetraene.*

By William O. Jones.

A new solid *cyclo*octatetraene dimer, $C_{16}H_{16}$, m. p. 38·5°, has been isolated. It has two double bonds and yields a compound, $C_{16}H_{20}$, m. p. 44·5°, on complete hydrogenation. The previously known solid dimer has been partially reduced to an unsaturated liquid hydrocarbon, $C_{16}H_{20}$. Possible structures are suggested. The dimers form crystalline adducts with silver nitrate.

Two dimers of *cyclo*octatetraene have been described by Reppe and his co-workers (*Annalen*, 1948, **560**, 1; B.I.O.S. Final Report No. 137, Appendix). By prolonged boiling under reflux in an atmosphere of nitrogen, a viscous liquid dimer was obtained, of b. p. 150°/4 mm., n_D^{20} 1·5856, which gave a solid, saturated hydrocarbon, $C_{16}H_{20}$, m. p. 33—35°, on hydrogenation. When *cyclo*octatetraene was boiled under reflux in air, either alone or in solution in *o*-dichlorobenzene, a mixture of two dimers was produced, one of which was a solid, m. p. 43°, whilst the other was regarded as identical with the liquid dimer obtained in nitrogen. The solid dimer absorbed three molecular proportions of hydrogen to give a liquid, $C_{16}H_{22}$, b. p. 127°/0·2 mm.

On repetition of the preparation in *o*-dichlorobenzene, dimeric products were obtained in slightly better yield. The melting point of the principal solid dimer however could not be raised above 41·5°. The liquid dimer had n_D^{20} 1·6030, appreciably higher than the value given by Reppe, and has now been shown to be a mixture of at least four substances.

We have also repeated the dimerisation of *cyclo*octatetraene in the absence of a solvent in a nitrogen atmosphere, and in this case obtained a product (f. p. 13°) with the lower

refractive index, n_D^{20} 1·5890. This material consists almost entirely of a new solid dimer, m. p. 38·5°, which we had previously prepared by boiling *cyclo*octatetraene with diethylaniline. It contains two double bonds and on catalytic hydrogenation yields a solid hydrocarbon, $C_{16}H_{20}$, m. p. 44·5°.

The dimer, m. p. 41·5°, was known to absorb three mols. of hydrogen when reduced in the presence of palladium–charcoal (Reppe, *loc. cit.*), the third mol. being taken up more slowly than the first two. We now find that with a palladium–barium carbonate catalyst, hydrogenation ceases after the absorption of two mols. of hydrogen, and a new compound, $C_{16}H_{20}$, can be isolated. This is still unsaturated, and, by use of a platinum oxide catalyst, can be converted into a fully saturated hydrocarbon, $C_{16}H_{22}$, identical with that described by Reppe.

The ultra-violet absorption spectra of the solid dimers, m. p. 41·5° and 38·5°, merely showed end-absorption beyond 2550 and 2240 Å respectively.

The dimers give high yields of fairly stable crystalline adducts with silver nitrate, and through their agency the original liquid dimers have been shown to be mixtures, and the individual dimers have been regenerated in a high state of purity by treatment of the adducts with ammonia.

The dimer of m. p. 41·5° forms two adducts, with 1 and 2 mols. respectively of silver nitrate, of m. p. 153° and 176° respectively (both explode at 192°). The 1 : 1 adduct can be converted into the 1 : 2 adduct by recrystallisation from glacial acetic acid or from aqueous 50% silver nitrate.

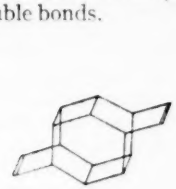
The new dimer (m. p. 38·5°) forms a 1 : 1 adduct with silver nitrate which melts at 196° and does not explode at temperatures up to 240°.

The apparent liquid dimer from the diethylaniline route is in fact the slightly impure 38·5° dimer since it gives over 90% of the calculated yield of a silver nitrate adduct, m. p. 194°, identical with that obtained from the solid dimer, and from which solid dimer of m. p. 36—38° can be recovered. We have not been able to isolate and purify the small amount of accompanying dimeric material which depresses the melting point. The same can be said of the liquid dimer obtained by heating *cyclo*octatetraene in a nitrogen atmosphere, which gave over 85% yields of the adduct, m. p. 194°.

The liquid portion of the dimer formed in *o*-dichlorobenzene is complex and has not been fully resolved. Both the solid dimers are present and, surprisingly, the hydride of the new solid dimer in small amount. Another dimer which gives an adduct, $C_{16}H_{16}.2AgNO_3$, m. p. 154—156°, is also probably present.

The dimer obtained by the diethylaniline route is the only one which appears to form an adduct with cuprous chloride–ammonium chloride, but this addition has not been examined closely.

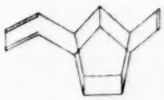
Thus, the dimerisation of *cyclo*octatetraene can give two dimers each containing two double bonds and one dimer containing three double bonds. Reppe regards the dimerisation as a diene synthesis, and for the dimers containing two double bonds he put forward structures such as (I) or (II). He made no suggestion in regard to a dimer with three double bonds.



(I)

(II)

(III)



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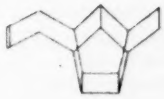

(V)

A dimer with three double bonds could be conceived as arising from a diene synthesis between one molecule of *cyclo*octatetraene as such and one molecule of the isomeric *bicyclo*[4 : 2 : 0]octa-2 : 4 : 7-triene. This would first give a product (III) with five double bonds, and a second intramolecular diene synthesis would then give a product (IV) with three double bonds. Further, two of these double bonds are conjugated (in the eight-membered ring), and, possibly, on hydrogenation 1 : 4-addition occurs first, as well as hydrogenation of the isolated double bond in the six-membered ring. Thus the partially saturated hydride is formulated as (V). The ability of an eight-membered ring to hydrogenate and retain one double bond is shown by *cyclo*octatetraene which can be converted into *cyclo*octene in virtually quantitative yield (Reppe, *loc. cit.*).

It is also possible that dimers containing three double bonds can have been formed by a doubling of the molecule through hydrogen transfer, followed by an intra-molecular Diels–Alder reaction.

Experimental

cyclo*Octatetraene in Boiling* o-*Dichlorobenzene.*—Freshly distilled *cyclo*octatetraene (300 g.; f. p. −5·0°) and freshly distilled *o*-dichlorobenzene (750 g.) were boiled together under reflux for 48 hr., then fractionated *in vacuo*, yielding unchanged *cyclo*octatetraene (75 g.), mixed dimers, b. p. 80—108°/0·15 mm., n_D^{20} 1·6030 (190 g., 63% conversion), and residue (34 g.). The mixed dimers were refractionated through a Vigreux column. The main fraction (105 g.), b. p. 115—125°/0·7 mm., n_D^{17} 1·6060, formed laths, m. p. 41·5°, after several crystallisations from ether and from ethanol (Found: C, 92·1; H, 7·8. Calc. for $C_{16}H_{16}$: C, 92·3; H, 7·7%). The forerun in the distillation (76 g.; n_D^{17} 1·5983) could not be obtained solid.

Boiling cyclo*Octatetraene in a Nitrogen Atmosphere.*—*cyclo*Octatetraene (20 g.) was heated at 150—160° for 48 hr., during which a slow current of nitrogen was passed into the liquid. The product, on vacuum distillation, yielded unchanged *cyclo*octatetraene (4 g.), dimer (7 g.), b. p. 95—100°/0·5 mm., f. p. +13°, n_D^{20} 1·5890, and an orange resin which was not distilled.

cyclo*Octatetraene in Boiling Nitrobenzene.*—*cyclo*Octatetraene (100 ml.) and freshly distilled nitrobenzene (200 ml.) were refluxed on a sand-bath for 64 hr. A small amount of water was formed. *cyclo*Octatetraene (15 ml.) and nitrobenzene (165 ml.) were then recovered by distillation *in vacuo*. The recovered nitrobenzene gave positive tests for aniline. The residue was a black pitch, which hardened to a brittle solid, readily soluble in hot benzene, moderately in acetone and sparingly in ethanol.

cyclo*Octatetraene in Boiling Diethylaniline.*—*cyclo*Octatetraene (253 g.) and diethylaniline (550 ml.) were boiled under reflux for 24 hr. Distillation then gave *cyclo*octatetraene (29 g.), dimers, b. p. 90—105°/0·5 mm. (158 g.), and residue (45 g.). Fractional distillation of the crude dimers yielded 120 g., of n_D^{20} 1·5866, b. p. 85—95°/0·2 mm., most of which solidified (m. p. 28°) after about an hr. The m. p. of this *dimer* was raised to 36° after five crystallisations from ethanol (Found: C, 92·2; H, 7·6. $C_{16}H_{16}$ requires C, 92·3; H, 7·7%). The new dimer is readily soluble in light petroleum, benzene, chloroform, and *iso*amyl alcohol, and moderately soluble in methanol, ethanol, and acetic acid. The m. p. was depressed to below 15° on admixture with the dimer of m. p. 41·5°.

In another preparation wherein heating was for 64 hr., there was no unchanged *cyclo*octatetraene, the yield of dimers was 71%, and there was an increased amount of high-boiling residue.

Hydrogenation of Dimer, m. p. 41·5°.—The dimer (30 g.) was hydrogenated in a stainless steel rotating autoclave with 1·2% palladium–barium carbonate (6 g.), benzene (70 ml.), and methanol (130 ml.) at 106°/100 atm. for 28 hr. The catalyst and solvents were removed, and the residue distilled at 88°/0·05 mm. After redistillation at 99—100°/0·15 mm. and 130—133°/2 mm., the *hydride* had n_D^{21} 1·5725 (Found: C, 90·8, 90·7; H, 9·5, 9·6. $C_{16}H_{20}$ requires C, 90·5; H, 9·5%).

This hydrocarbon decolorized bromine in carbon tetrachloride, and a sample (2·942 g.) absorbed 280 ml. (0·90 mol.) of hydrogen in 50 min. at room temperature in the presence of pre-reduced platinum oxide (0·046 g.) in *cyclo*hexane (50 ml.). After distillation *in vacuo* (b. p. 171—172°/10 mm.), a colourless liquid (2·5 g.) was obtained, having f. p. −15°, n_D^{17} 1·5665 (Found: C, 89·7; H, 10·1. Calc. for $C_{16}H_{22}$: C, 89·7; H, 10·3%).

Hydrogenation of Dimer, m. p. 38·5°.—The dimer (6·57 g.) was shaken in methanol (100 ml.) with hydrogen in the presence of platinum oxide (0·2 g.). A white crystalline material soon separated and caused the catalyst to coagulate. Ethanol (50 ml.) was then added, and the

mixture warmed to 55°, complete solution being obtained. A further 0·2 g. of catalyst was added and hydrogenation continued at 50°. Absorption ceased after 1130 ml. (1·6 mols.) of hydrogen had been taken up. On cooling, the saturated *hydrocarbon* crystallised in prisms, which melted at 44·5° after repeated recrystallisation from alcohol and then from acetone (Found: C, 90·8, 90·7; H, 9·4, 9·4. $C_{16}H_{20}$ requires C, 90·5; H, 9·5%).

Silver Nitrate Adduct from Dimer, m. p. 41·5°.—Silver nitrate (1·71 g.) in ethylene glycol (5 ml.) was added to the dimer (2·08 g.) in absolute ethanol (50 ml.) and the mixture boiled for 2 min. The *adduct* (2·74 g.), obtained on cooling, crystallised from ethanol in prisms, m. p. 153° (Found: Ag, 28·1. $C_{16}H_{16}$,$AgNO_3$ requires Ag, 28·5%). Silver was determined by warming the adduct with concentrated nitric acid, dilution with water, and titration with potassium thiocyanate. Carbon and hydrogen values could not be obtained on any of the silver nitrate adducts because of violent decomposition on heating. The present adduct exploded in a capillary m. p. tube when the temperature reached 192°. On recrystallisation from glacial acetic acid or 50% aqueous silver nitrate, a new *adduct* was obtained, having m. p. 176° (explodes at 190°) (Found: Ag, 39·2. $C_{16}H_{16}$,$2AgNO_3$ requires Ag, 39·4%). The dimer was regenerated by warming the 1 : 2 adduct (28 g.) slightly with concentrated aqueous ammonia (100 ml.). The liberated oil, when taken up in ether, washed, dried, and distilled, had b. p. 115—118°/0·7 mm., m. p. 41·0°, n_D^{22} 1·6075.

A homogeneous solution was obtained when the dimer was warmed with 25—50% aqueous silver nitrate, and one or other of the above adducts separated on cooling, depending on the amount of silver nitrate employed. In the first experiment, with excess of silver nitrate, colourless, feathery needles, m. p. 182°, were obtained, but all subsequent experiments yielded the modification melting at 176°.

Silver Nitrate Adduct from Dimer, M. P. 38·5°.—When a solution of silver nitrate (0·7 g. in 35 ml. of ethanol) was added to the dimer (0·8 g. in 10 ml. of ethanol) a white powder was immediately precipitated. After boiling for 5 min., the mixture was cooled and filtered, and the solid was washed with ethanol and with ether and air-dried. The *adduct* (1·05 g.) had m. p. 196° (Found: Ag, 28·4%). The melted specimen did not decompose explosively at temperatures up to 230°. There was a gradual loss of dimer on prolonged heating at 110°, the silver content being 30% after 18 hr. at this temperature.

The same adduct was formed in quantitative yield when the dimer was treated with aqueous silver nitrate (25%). Variation of the silver nitrate : dimer ratio from 3 : 1 to 1 : 1 always resulted in the formation of the 1 : 1 adduct.

By treatment of the adduct with ammonia, the dimer was recovered in a very pure form, b. p. 101—103°/0·25 mm., m. p. 38·5°.

Silver Nitrate Adduct from the Liquid Dimer from the Diethylaniline Route.—The liquid (n_D^{22} 1·5828) employed was a mixture of the fore-run obtained on re-distillation of the crude dimer, and the oil obtained when the solid was filtered off from the main fraction. The dimer (17·9 g.) was warmed on the steam-bath for 10 min. with 3 mols. of aqueous silver nitrate (50%). The grey precipitate was washed with ethanol and with ether, and dried (29 g.; m. p. 191—192°). The m. p. was raised to 193° by one crystallisation from 50% silver nitrate and a mixture with the above 196° adduct melted at 193—195°. Reaction in ethanol–ethylene glycol gave a purer product in a somewhat smaller yield (81%; m. p. 195°).

Regeneration of the dimer by means of ammonia gave an 85% recovery of material, m. p. 28—29°, from which the dimer, m. p. 38·5°, could be obtained by redistillation.

Silver Nitrate Adduct from the Liquid Dimer obtained by heating cyclo*Octatetraene in Nitrogen.*—The dimer (1·0 g.) was warmed at 90° for 2 min. with silver nitrate (2·5 g.) and water (2·5 g.). The white powder produced (1·6 g., 88%) had m. p. 191°, raised to 196° on extraction with hot ethanol, not depressed on mixing with the adduct obtained from the dimer of m. p. 38·5°.

Silver Nitrate Adduct from the Liquid Dimer from the o*-Dichlorobenzene Route.*—This dimeric material behaved very differently from those hitherto described in that there was no separation of adduct when the reaction was carried out in alcohol. (i) When a fraction, b. p. 90—100°/0·7 mm., n_D^{17} 1·6008 (23·9 g.), was added to 3 mols. of 50% aqueous silver nitrate at room temperature there was an immediate formation of an extremely viscous oil. After being kept overnight the major portion had formed colourless crystals, but there still remained a lump of pale brown gum. The crude adduct (58 g., 92%) was boiled with chloroform (200 ml.) and filtered. The residue (2 g.; m. p. 38—40°) obtained after removal of the solvent did not absorb bromine or hydrogen and its m. p. was not depressed on admixture with the hydride obtained from the dimer of m. p. 38·5° (Found: C, 90·3; H, 9·8. Calc. for $C_{16}H_{20}$: C, 90·5; H, 9·5%). The solid adduct remaining after the chloroform treatment was heated to the b. p. with

25% silver nitrate solution (400 ml.) and filtered hot. The undissolved portion (4 g.; m. p. 194°) was shown to be identical (by mixed m. p. of the adduct and of the regenerated dimer) with the adduct obtained from the dimer of m. p. 38·5°. Large, colourless plates (23 g.; m. p. 154°, explodes at 190°) separated when the aqueous silver nitrate extract was cooled. The m. p. was depressed slightly (146—148°) after admixture with the previously described adduct of m. p. 153°, and the non-identity of the two adducts was confirmed by the much higher silver content of the present adduct (Found: Ag, 38·8. $C_{16}H_{16}.2AgNO_3$ requires Ag, 39·4%). (ii) In another preparation, with the dimer fraction of b. p. 85—90°/0·7 mm., n_D^{17} 1·5958 (18·8 g.), the crude adduct (33·1 g.) by tedious fractional crystallisation from ethanol and from 50% aqueous silver nitrate gave the adduct of m. p. 195° (21·6 g.), the adduct of m. p. 176° (6 g.), several fractions in the melting range 153—163° (Ag values about 33%), and an oil (0·3 g., n_D^{24} 1·590) which had not combined with silver nitrate.

Cuprous Chloride–Ammonium Chloride Addition Compound with cyclo*Octatetraene Dimer.*—The only dimer which appeared to react was that produced by the diethylaniline route, and this formed a bulky yellowish-green solid when shaken with the reagent. The adduct was insoluble in boiling ethanol and in toluene; it was not stable in boiling acetic acid. It does not possess a definite m. p.; it darkens at about 160—170° in a capillary tube, and dimer refluxes at about 250°.

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416. *Nucleotides. Part XXI.* The Action of Ribonuclease on Simple Esters of the Monoribonucleotides.*

By D. M. Brown and A. R. Todd.

Preparation of uridine benzyl phosphates *a* and *b* as their mixed barium salts, barium uridine benzyl phosphate *b*, and the two crystalline isomers, cytidine benzyl phosphate *a* and *b* is described. Ribonuclease is found to effect hydrolysis of the *b* isomers only, yielding uridylic and cytidylic acids *b*, *via* the corresponding cyclic nucleoside-2′ : 3′ phosphates. Other comparable observations with methyl and ethyl esters are described. Benzyl esters of the adenylic acids and of uridine-5′ phosphate are not attacked by ribonuclease.

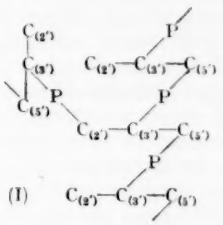
The mechanism and specificity of ribonuclease action are discussed in relation to chemical hydrolytic mechanisms. Structural features of the ribonucleic acids are discussed in the light of these observations.

The problem of the structure of macromolecular substances is complicated by the great number of theoretically possible isomers. In the case of the ribonucleic acids this isomerism might arise not only from the arrangement of the four constituent nucleotides, but also from the possible variety of phosphodiester internucleotidic linkages involving the 2′-, 3′-, and 5′-positions in the nucleoside residues. In an earlier publication (Brown and Todd, Part X, *J.*, 1952, 52) general structures for the ribonucleic acids were discussed and (I), in which the extent of chain-branching is unspecified, was put forward as a working hypothesis to be tested by further experiment. This structure was reached from consideration of the constitution of the mononucleotides derived from chemical and enzymic hydrolysates of nucleic acids and of the mechanism of the hydrolytic processes involved.

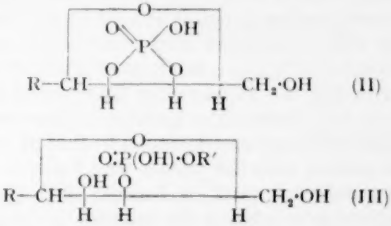
When ribonucleic acids are hydrolysed with alkali, the only products are the 2′ and 3′ phosphates of the nucleosides, adenosine, guanosine, uridine, and cytidine. These, it was held, were produced by way of the intermediate nucleoside-2′ : 3′ phosphates, by a mechanism for which adequate analogies were available. One important conclusion which emerged was that the hydrolysis of an ester of a mononucleotide (*e.g.*, III) should yield a mixture of the 2′ and the 3′ nucleotide regardless of the position of the phosphoryl group

* Part XX, *J.*, 1953, 951.

(2′ or 3′) in the original diester. Experimentally, adenosine benzyl phosphate *a* or *b* with sodium hydroxide yielded a mixture of adenylic acids *a* and *b* (Brown and Todd, Part IX, *J.*, 1952, **44**), and synthetic nucleoside-2′ : 3′ phosphates (Brown, Magrath, and Todd, *J.*, 1952, 2708) likewise yielded mixtures of the *a* and *b* mononucleotides under mild conditions. Because of these facts we pointed out (Part X) that structures for the ribonucleic acids differing from (I) in that $C_{(2')}$–$C_{(5')}$ internucleotide linkages are present, would in theory, be equally admissible, since the products of hydrolysis would be the same in either case.



(I)



(II)

(III)

The true orientation of the phosphoryl group in the *a* and *b* isomers of the mononucleotides has not been fully established although physical evidence for the view that cytidylic acid *b* is cytidine-3′ phosphate has been advanced (Loring, Hammell, Levy, and Bortner, *J. Biol. Chem.*, 1952, **196**, 821; Cavalieri, *J. Amer. Chem. Soc.*, 1952, **74**, 5804). At present it will be most convenient to discuss whether *a*-$C_{(5')}$ or *b*-$C_{(5')}$ linkages, or both types, are present in the ribonucleic acids. Clearly, the arguments given above show that hydrolyses by acid or alkali at least in their present form do not permit any distinction to be made between the *a* and the *b* positions of the nucleoside residues as linkage points in the polynucleotides. We did, however, make the significant observation (Brown, Dekker, and Todd, *J.*, 1952, 2715) that both cytidine-2′ : 3′ phosphate and uridine-2′ : 3′ phosphate are hydrolysed by the enzyme ribonuclease, yielding only the *b* isomers of cytidylic acid and of uridylic acid. We discussed the relation between these observations and those made by others (*inter al.*, Markham and Smith, *Nature*, 1951, **168**, 406; Schmidt *et al.*, *J. Biol. Chem.*, 1951, **192**, 715) on the structure of the end-products of ribonuclease hydrolysis of ribonucleic acids, and their transformation products. The opening of the cyclic phosphoryl group was evidently the secondary action of the enzyme; the rupture of phosphodiester internucleotide linkages to yield products bearing the cyclic phosphoryl group was apparently its initial action. We decided to study this initial action, again using synthetic substrates whose structures could be closely defined. Particularly, it was considered necessary to prepare and study esters of the *a* and *b* nucleotides which could be related to the parent nucleotide by means other than hydrolysis. Benzyl esters were chosen since it was expected that hydrogenation would convert them into the free nucleotide without phosphoryl migration (cf. Brown, Abstr. Papers 2nd Internat. Congr. Biochem., Paris, 1952, p. 253; Todd, *Angew. Chem.*, 1953, **65**, 12).

By treating mixed adenylic acids *a* and *b* with phenyldiazomethane in dimethylformamide it was possible to prepare adenosine benzyl phosphates *a* and *b* in fair yield (Part IX). Application of this procedure to ordinary yeast uridylic acid and yeast cytidylic acid yielded analogously uridine benzyl phosphate and cytidine benzyl phosphate, isolated in the crude state as their barium salts. When treated with alkali they were hydrolysed to the corresponding mononucleotide mixture, as were the adenosine derivatives (Part IX).

When barium cytidine benzyl phosphate was treated with ribonuclease and the reaction followed on paper chromatograms it was found that hydrolysis of the ester occurred and cytidylic acid accumulated. Furthermore, cytidine-2′ : 3′ phosphate, which was present only in traces in the starting material, persisted in the solution at an approximately constant concentration during the hydrolysis and then disappeared when hydrolysis was complete. This was good evidence that cytidine-2′ : 3′ phosphate was an intermediate in the hydrolysis. In these experiments it was noticed that the spot on the chromatograms corresponding to the benzyl ester never disappeared completely, even after exhaustive

treatment with ribonuclease. Exactly comparable observations were made during the treatment of uridine benzyl phosphate with ribonuclease; uridine-2′ : 3′ phosphate was present in the solution during the hydrolysis and disappeared at the end, while some benzyl ester remained after prolonged treatment.

These phenomena were studied more closely by analysis of the materials before and after treatment with ribonuclease on a strong base anion-exchange column (Dowex-2). The crude preparation of barium cytidine benzyl phosphate, when analysed on the ion-exchange column with 0·02N-formic acid as eluant, showed several minor peaks, including two corresponding to cytidylic acid *a* and *b* (and the coincident cyclic phosphate). Further elution with 0·1N-formic acid removed the two major components, evidently the *a* and *b* benzyl esters (Fig. 1). Analysis of ribonuclease-treated material gave the elution diagram shown in Fig. 2. It was clear that one of the esters was hydrolysed and converted into cytidylic acid *b* since the position of the new peak and the optical density ratio over the peak (280/260 mμ) corresponded to that of the *b*-acid assessed by previous standardisation of the column with the pure *a*- and *b*-acids. Moreover, by integrating the optical-density units under each peak, it become clear that after the enzymic hydrolysis there was a correspondence between the increase in the cytidylic acid *b* peak and the disappearance of one of the benzyl ester peaks, while the other ester component did not change in quantity as estimated by this method. These estimations were semiquantitative and hence only indicative, since it was assumed that all the substances involved had the same extinction coefficient.

The mixed cytidine benzyl phosphates were prepared on a larger scale and by ion-exchange chromatography it was possible to isolate the two benzyl esters in pure crystalline form. The ester which was eluted first was oriented by hydrogenation over palladium oxide. It yielded a product which when analysed on the ion-exchange column was found to be cytidylic acid *a*; the ester was therefore cytidine benzyl phosphate *a*. It was found to be completely unaffected by ribonuclease. The second ester removed from the column gave the ion-exchange analysis diagram shown in Fig. 3. Hydrogenation gave cytidylic acid *b* (Fig. 4), showing that the ester was cytidine benzyl phosphate *b*. Treatment with ribonuclease also resulted in complete conversion into cytidylic acid *b* (Fig. 5). In the last experiment, paper chromatography showed that shortly after the start of the hydrolysis cytidine-2′ : 3′ phosphate was present in the solution although it could not be detected in the starting material or at the end of the hydrolysis. When cytidine benzyl phosphate *b* was set aside in 0·5N-sodium hydroxide at 37° overnight it yielded a solution which was shown by ion-exchange chromatography to contain only cytidylic acids *a* and *b* (*ca.* 40% and 60% respectively) in accord with the phosphoryl migration observed during the hydrolysis of adenosine benzyl phosphates *a* and *b* (Part IX).

When the barium salt of uridine benzyl phosphate was analysed on the ion-exchange column two peaks were observed, presumably corresponding to the ester components, together with a minor one due to contamination by uridine-2′ : 3′ phosphate (Figs. 6 and 8). Analysis of ribonuclease-treated material gave the elution diagram shown in Fig. 7, from which it could be seen that the major ester component (and the small amount of cyclic phosphate) had been converted into uridylic acid *b* (the position of which was known by prior standardisation of the column with uridylic acids *a* and *b*). The ester present in smaller amount (20—24%) was apparently unaffected by the enzyme. The difficulty of separating and isolating the two esters in a pure form, due mainly to the high ionic strengths of the buffers required to remove them from the ion-exchange resin, made it necessary to characterise them by other means. The mixed esters as their barium salts (20 mg.) were treated with ribonuclease and incubated until reaction was complete. The solution was applied to a paper strip and chromatographed in the *iso*propyl alcohol–water–ammonia system. Uridylic acid remained near the origin and the unchanged benzyl ester (R_F, 0·6; *ca.* 3—4 mg.) was eluted from the paper and the solution hydrogenated over palladium oxide. Ion-exchange analysis of the product showed that it was entirely uridylic acid *a*. It followed that the ester which was not attacked by ribonuclease was uridine benzyl phosphate *a* and that which was hydrolysed was uridine benzyl phosphate *b*. Confirmation of this was obtained by using another preparation of barium uridine benzyl phosphate

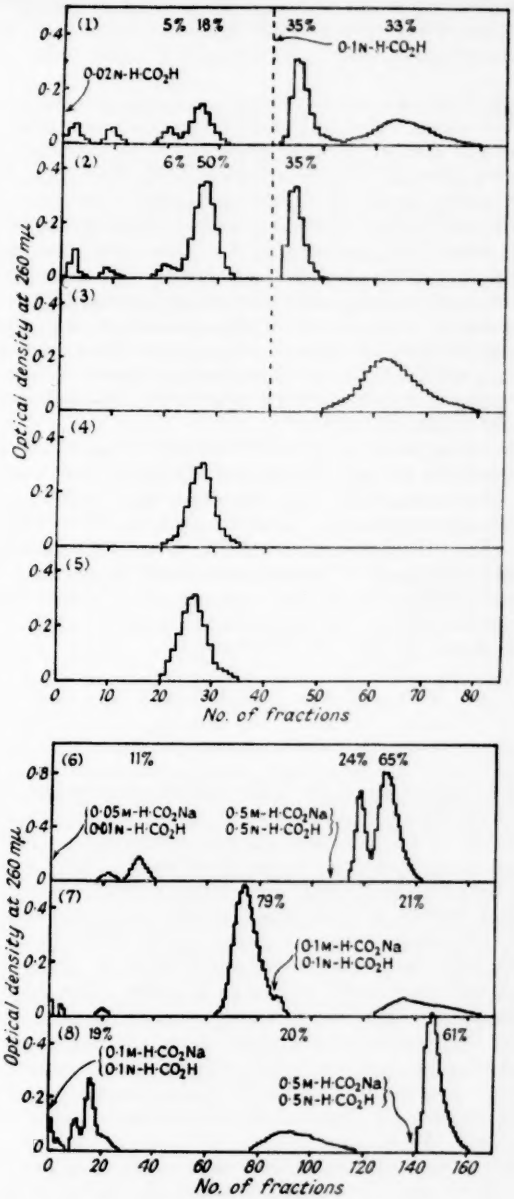


FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIG. 5

FIG. 6

FIG. 7

FIG. 8

Ion-exchange analysis diagrams of :

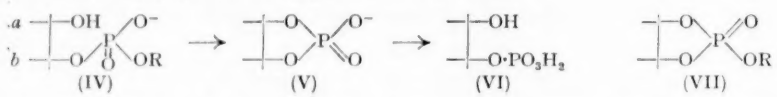
(1) Cytidine benzyl phosphates *a* and *b*. (2) Product of action of ribonuclease on (1). (3) Cytidine benzyl phosphate *b*. (4) Hydrogenation product from (3) (cytidylic acid *b*). (5) Product of ribonuclease action on (3). (6) and (8), Uridine benzyl phosphates *a* and *b*. (7) Product from ribonuclease action on (6).

Figures relative to peaks represent the optical density units in each peak as a percentage of total optical density units eluted. In standard runs cytidylic acids *a* and *b* had peaks at fractions 21 and 28 respectively, and uridylic acids *a* and *b* at fractions 60 and 71 respectively.

prepared under milder conditions from crystalline uridylic acid *b* (kindly provided by Mr. D. I. Magrath). This material was completely hydrolysed to uridylic acid by ribonuclease (paper-chromatographic examination) and on hydrogenation gave only uridylic acid *b* (ion-exchange analysis).

In addition to the above experiments using benzyl esters some observations have been made with other simple alkyl esters. Cytidine methyl phosphate (see below) was readily hydrolysed by the enzyme and showed the same phenomenon as the benzyl esters, *viz.*, a small amount was unaffected after exhaustive treatment. Mr. D. I. Magrath has found (in unpublished work) that uridine methyl phosphate and uridine ethyl phosphate (Brown, Magrath, and Todd, *loc. cit.*) are hydrolysed by ribonuclease, again leaving a small amount of material unaffected. It seems very probable that in these cases, too, the *b* isomer is hydrolysed, while the *a* isomer is stable towards the enzyme. The close analogy with the benzyl esters makes this likely and we feel justified in utilising this reactivity of esters of the *b*-pyrimidine nucleotides towards ribonuclease for the orientation of compounds of this type whose structures cannot otherwise be defined. To complete the model experiments on the specificity of the enzyme, uridine-5′ benzyl phosphate, adenosine-5′ benzyl phosphate, and adenosine benzyl phosphates *a* and *b* were treated with ribonuclease. In no case could evidence of reaction be obtained.

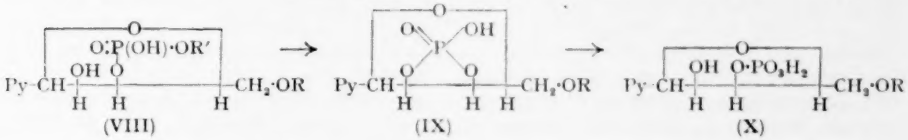
The implications of the above observations must now be assessed, first, regarding the intimate action of the enzyme and, secondly, as an aid to the further structural elucidation of the ribonucleic acids. Ribonuclease acts as a diesterase specifically hydrolysing esters of the *b*-isomers of the pyrimidine nucleotides. The observable sequence follows that given in the partial formulæ (IV—VI). The initial reaction (IV) ⟶ (V) is formally equivalent to a trans-esterification in which the $C_{(a)}$-O–P bond is formed with elimination of the esterifying group (R) as the alcohol, ROH. The second, slower reaction involves the hydrolysis of the cyclic phosphoryl group in this case by fission of the $C_{(a)}$-O–P bond. The nature of the esterifying group (R) does not appear to be important.



In essence the enzymic hydrolysis is similar to that which we proposed for the chemical hydrolysis of nucleotide esters (Part X) with the exception that the enzyme is more specific in that it attacks only esters of the *b*-isomers of the pyrimidine nucleotides. In our earlier discussion of the chemical hydrolysis we invoked for simplicity in representation an intermediate to which we gave the classical formulation (VII); this then broke down, yielding (V) and the alcohol, ROH. It seems likely that the chemical hydrolytic process depends on the attack by the vicinal hydroxyl group on the P=O bond, catalysed by hydrogen or hydroxyl ions, with simultaneous removal of R as an alkoxy-anion, possibly with the intervention of a quinquecovalent transition complex. The enzymic hydrolysis probably proceeds in a similar manner, the formation, and subsequent cleavage, of the $C_{(a)}$-O–P bond representing the fundamental catalytic steps. Since the first step proceeds without increase in the number of phosphoryl dissociations, this may represent the rapid initial "depolymerisation" observed in the action of the enzyme on ribonucleic acids during which no titratable groups are liberated (cf. Chantrenne, Linderstrøm-Lang, and Vandendriessche, *Nature*, **1947**, **159**, 877).

When ribonuclease acts on ribonucleic acids the first products have properties consistent with the structure (IX; Py = uracil or cytosine residue; R = H or remainder of polynucleotide chain) (Markham and Smith, *loc. cit.*; *Biochem. J.*, 1952, **52**, 552, 558). As a further action, ribonuclease then opens the cyclic phosphoryl groups, yielding products of the general type (X; R = H or remainder of the polynucleotide chain) in which the terminal phosphoryl group occupies the *b*-position in the pyrimidine nucleoside residue (Brown, Dekker, and Todd, *loc. cit.*). The work described here leads to the conclusion that the first action of the enzyme is to cleave phosphodiester linkages to products of type (IX; Py= uracil or cytosine residue; R = H or remainder of polynucleotide chain). Furthermore,

the nature of the specificity as shown here with substrates of defined structure permits the conclusion that such cleavage should occur only at pyrimidine nucleotide residues which are linked at the *b*-position through a phosphoryl group to the next nucleoside residue (R′) as in (VIII); the identification of the *b* with the 3′-position in the pyrimidine nucleotides is supported by the physical data obtained by Loring, Hammell, Levy, and Bortner



(*loc. cit.*) and by Cavalieri (*loc. cit.*) for the isomeric cytidylic acids. For the reaction sequence (VIII) ⟶ (X) to be possible, the remainder of the polynucleotide chain (R in VIII) must be linked at the $C_{(5')}$-position of the pyrimidine nucleotide residue. The work of others (*inter al.*, Schmidt *et al.*, *J. Cell. Comp. Physiol.*, 1951, Suppl. 1, **38**, 61; *J. Biol. Chem.*, 1951, **192**, 715; Markham and Smith, *loc. cit.*; Cohn, personal communications) shows that all, or almost all, of the pyrimidine nucleotide residues involved in diester linkage in the ribonucleic acids are affected during ribonuclease action, so that at all these positions in the intact molecule the structure is of the form (VIII; R = R′ = polynucleotide chain). This does not preclude a similar situation existing at purine nucleotide sites in the nucleic acid molecule since the stability of the esters of the adenylic acids towards ribonuclease provides evidence that the previously assumed pyrimidine specificity is correct and does not depend on a difference in linkage point on the purine nucleoside residues. Other evidence supports the view that the purine nucleoside residues are linked at the *b*(or *a*)- and $C_{(5')}$-positions [VIII; Pu (=purine residue) in place of Py· (Part X, *loc. cit.*; Cohn and Volkin, *Nature*, 1951, **167**, 483; *Arch. Biochem. Biophys.*, 1952, **35**, 465; Merrifield and Woolley, *J. Biol. Chem.*, 1952, **197**, 521], and hydrolytic experiments with spleen nuclease suggest that here also the *b*-position is favoured (Volkin and Cohn, *Fed. Proc.*, 1952, **11**, 303).

It should, of course, be borne in mind that although the phosphoryl groups in uridylic acid *b* and cytidylic acid *b* occupy the same position (probably 3′) in the sugar residue (Loring and Luthy, *J. Amer. Chem. Soc.*, 1951, **73**, 4215; Brown, Dekker, and Todd, *loc. cit.*) no clear evidence exists as yet to show that the phosphoryl group is similarly located in the *b* isomers of the purine nucleotides.

The experiments described in this paper clarify the specificity and mode of action of crystalline pancreatic ribonuclease. They also provide additional confirmation for the general structural pattern (I) of the ribonucleic acids advanced by us in Part X, and limit the linkage of the pyrimidine nucleoside residues to the *b* position; they provide no further information about the position of linkage in the purine nucleoside residues. In Part X we discussed other types of internucleotidic linkage than that adopted in structure (I). Of these other types the exclusion of $C_{(5')}$–$C_{(5')}$ as a possibility on chemical grounds has since been justified by study of a synthetic dinucleoside-5′ : 5′ phosphate (Elmore and Todd, *J.*, 1952, 3681). As regards $C_{(2')}$–$C_{(3')}$ linkage, it was pointed out that in such a case alkaline hydrolysis, proceeding as it does through a cyclic intermediate, could only occur stepwise from the end of the chain. If we accept the findings of other workers on the nature of the end-products of ribonuclease action and the results obtained by Merrifield and Woolley (*loc. cit.*) by acid hydrolysis of ribonucleic acids, our own observations on ribonuclease action virtually exclude $C_{(2')}$–$C_{(3')}$ as an internucleotidic linkage save between a residue in the main chain and the first residue in a side-chain or branch. They do not, of course, permit any conclusion as to the occurrence or extent of chain-branching, but they do reinforce our earlier view (Part X) that if chain-branching (other than branching on phosphorus) occurs it can only do so in the manner indicated in (I), *i.e.*, the first residue in the branch must be a pyrimidine nucleoside linked through its *b* position to a residue in the main chain.

One observation has been made, unconnected with the main problem, which deserves

mention. When cytidylic acid was treated with phenyldiazomethane in dimethylformamide the reaction was very slow, owing, probably, to the very low solubility of the nucleotide. During the large-scale preparation of cytidine benzyl phosphates *a* and *b* a considerable amount of methanol was added and the reaction rate increased markedly. The solution, when submitted to ion-exchange chromatography, afforded a material in considerable yield which was eluted from the column before the other main products. It crystallised well and gave analytical values corresponding to cytidine methyl phosphate. Chromatographic behaviour and hydrolyses with sodium hydroxide and with ribonuclease were in accord with this formulation. This observation recalls the disputed claim that treatment of stilbœstrol with diazomethane in presence of *iso*propyl alcohol yields di*iso*propylstilbœstrol (Schonberg and Mustafa, *J.*, 1946, 746; Gerber and Curtin, *J. Amer. Chem. Soc.*, 1949, **71**, 1499; Weygand and Kirchner, *Angew. Chem.*, 1952, **64**, 203).

Experimental

Paper Chromatography of the Nucleotide Derivatives.—The solvent system most widely used in the present investigation was *iso*propyl alcohol–ammonia–water (70 : 10 : 20 v/v). This gave excellent separation of the nucleotide esters from the corresponding nucleotides and nucleoside cyclic phosphates (cf. Brown, Magrath, and Todd, *loc. cit.*). Other solvent systems used are mentioned at the appropriate place in the text. Spots were detected by photographing the chromatograms in ultra-violet light. Standard substances were always run simultaneously for identification purposes.

Ion-exchange Analyses.—A column (11·2 × 1 cm.) of Dowex-2 (200—400 mesh) in the formate form was used throughout. A flow rate of approx. 0·5—0·7 c.c./min. was maintained by application of pressure. Fractions were collected in an automatic apparatus (syphon type, giving fractions of *ca.* 11·5 c.c.). The solutions used for the analytical separations of the cytidylic and uridylic acids and the corresponding cyclic phosphates have been described before (Cohn and Volkin, *locc. cit.*; Brown, Dekker, and Todd, *loc. cit.*). Solutions of greater eluting power were required to remove the nucleotide benzyl esters from the column. These are recorded in the Figures, where some elution diagrams are shown. As before, substances were identified by the number of fractions to the peak and, where applicable, by the optical density ratios (280/260 mμ) over the peak.

Cytidine Benzyl Phosphates a *and* b.—*Initial preparation.* Cytidylic acid (0·3 g.; prepared from yeast nucleic acid) was suspended in dimethylformamide (3 c.c.) and treated with phenyldiazomethane (from 2·3 g. of benzaldehyde hydrazone). After the mixture had been shaken overnight little reaction had occurred. A small amount of methanol was added, and after 12 hr. the mixture was homogeneous. Ether (40 c.c.) was added and the solvent decanted from the gum which separated. The gum was shaken with chloroform and water, and the aqueous layer further extracted with chloroform and then reduced in bulk. Saturated barium hydroxide solution (0·6 c.c.) was added, and the solution brought to neutrality with carbon dioxide, boiled, filtered, and reduced to small bulk. Addition of ethanol (40 c.c.) precipitated the product (58 mg.) which was collected by centrifugation. This material, which was not pure enough for analysis, was a crude mixture of barium cytidine benzyl phosphates *a* and *b* on evidence detailed below. It was used for enzymic experiments. Ion-exchange analysis of the material (3·5 mg.) gave the diagram shown in Fig. 1. Paper chromatography showed that it consisted of a major component—the benzyl esters (R_F 0·7)—together with traces of cytidylic acid (R_F 0·1) and cytidine-2′ : 3′ phosphate (R_F 0·4). When the material (4·0 mg.) was treated with 0·5N-sodium hydroxide (0·2 c.c.) at 37° for 15 hr. complete conversion into cytidylic acid was shown by paper chromatography.

Large-scale preparation. Cytidylic acid (0·75 g.) was treated with phenyldiazomethane (from 3·0 g. of benzaldehyde hydrazone) in a mixture of dimethylformamide (25 c.c.) and methanol (25 c.c.). After 36 hr. reaction was complete and the product was precipitated by addition of ether (400 c.c.). The gum was shaken with chloroform, water, and barium carbonate, and the aqueous phase was washed with more chloroform and evaporated to small bulk. Addition of much ethanol precipitated the crude barium salt (0·64 g.). A solution of the material (18 mg.) was brought to pH 8, and analysed on the ion-exchange column. In addition to the two benzyl ester peaks (cf. Fig. 1) another major product was observed (peak at fraction 10). This product was isolated (see below) and shown to be cytidine methyl phosphate. For large-scale separation the crude product (0·62 g.) was dissolved in water (50 c.c.), and the solution brought to pH 8 and run on to a column (10·5 × 3 cm.) of Dowex-2 resin (formate form).

After washing of the column with water, elution was commenced with 0·02N-formic acid. The first component (cytidine methyl phosphate) was removed (volume to peak, 400 c.c.) and the fractions containing this material were bulked and worked up (see below). Elution was continued until all mononucleotide and cyclic phosphate had been removed from the column. 0·1N-Formic acid then removed cytidine benzyl phosphate *a* from the column, and then cytidine benzyl phosphate *b* was rapidly eluted with 0·5N-formic acid.

The fractions containing cytidine methyl phosphate were pooled and evaporated under reduced pressure; the residue crystallised from water containing a little ethanol. *Cytidine methyl phosphate* separated in colourless irregular prisms (52 mg.), slowly melting, with decomp. from 210° (Found: C, 36·0; H, 4·6; N, 12·6; P, 9·0. $C_{10}H_{16}O_8N_3P$ requires C, 35·7; H, 4·8; N, 12·45; P, 9·2%). The material (1·0 mg.) was analysed on the ion-exchange column in 0·02N-formic acid. Only one peak was observed (at fraction 10) with an optical density ratio of 1·96. The substance had R_p 0·5 in the *iso*propyl alcohol–ammonia–water system. The material (0·05 mg.) was dissolved in 0·5N-sodium hydroxide (0·1 c.c.) and kept at 37° for 15 hr. Paper chromatography showed complete hydrolysis to cytidylic acid.

The fractions containing *cytidine benzyl phosphate* a were pooled and evaporated to dryness under reduced pressure below room temperature. The product crystallised from water containing a little ethanol in colourless needles (48 mg.). The hydrated material was dried for analysis at 105° for 24 hr. over phosphoric oxide. It sintered at 168° and melted at 174° (Found, C, 46·4; H, 5·1; N, 10·4; P, 6·8. $C_{16}H_{20}O_8N_3P$ requires C, 46·6; H, 4·9; N, 10·2; P, 7·5%).

The material (1·1 mg.) was hydrogenated over palladium oxide for 2 hr. at room temperature and pressure. The product was then analysed on the ion-exchange column in the usual way. The elution diagram showed only one peak corresponding in position (fraction 20) and optical density ratio (1·74) to that given by authentic cytidylic acid *a*.

The pooled fractions containing *cytidine benzyl phosphate* b were evaporated under reduced pressure below room temperature, water being added in the later stages of the evaporation to reduce the formic acid concentration. The product crystallised from water in small prisms (66 mg.), which slowly decomposed from 170° with final m. p. 203° (Found, in material dried at 105°/vac. over phosphoric oxide: C, 46·7; H, 5·0; N, 10·2; P, 7·1%).

The substance (1·5 mg.) when analysed on the ion-exchange column showed only one peak on the diagram (Fig. 3) with an optical density ratio of 1·85 over the peak.

Hydrogenation of the material (1·5 mg.) over palladium oxide gave one product identical with cytidylic acid *b* in its ion-exchange characteristics (Fig. 4; peak at fraction 28 with an optical density ratio of 2·0).

Cytidine benzyl phosphate *b* (1·5 mg.) was treated with 0·5N-sodium hydroxide (0·2 c.c.) at 37° for 15 hr. Paper chromatography showed that complete hydrolysis to mononucleotide had occurred. After neutralisation with formic acid and dilution, the solution was analysed on the ion-exchange column. Two peaks were observed corresponding to cytidylic acids *a* and *b* (40% and 60% of total optical density units with optical density ratios of 1·8 and 2·0 respectively.

Barium Uridine Benzyl Phosphates a *and* b.—Uridylic acid (0·5 g.) was partially dissolved in dimethylformamide (3 c.c.), and phenyldiazomethane (from 1 g. of benzaldehyde hydrazone) added. The violent reaction was modified by cooling and next morning ether (40 c.c.) was added. The precipitated gum was washed with more ether. The gum was dissolved in a little ethanol and diluted with ether. A small amount of sticky solid separated and was discarded. The mother-liquors were evaporated to dryness, then shaken with water and chloroform, and the aqueous phase was washed again with chloroform. Saturated barium hydroxide solution (2 c.c.) was added to the aqueous solution, then carbon dioxide was passed in to neutrality. The solution was reduced to 5 c.c. and filtered through Hyflo Supercel. Addition of ethanol did not produce significant precipitation of the product, so the aqueous-ethanolic solution was evaporated under reduced pressure. The solid foam was very hygroscopic and gave poor analytical values, but was used as such for the enzymic experiments [Found, in material dried at 50°/0·1 mm. over phosphoric oxide: C, 38·2; H, 3·9; N, 6·9; P, 6·2; Calc. for $(C_{16}H_{19}O_9N_2P)_2Ba$: C, 39·8; H, 3·8; N, 5·8; P, 6·4%].

Paper chromatography showed that this material gave one spot due to the benzyl esters (R_p 0·7) and another corresponding to a very small amount of uridine-2′ : 3′ phosphate (R_p 0·35). Ion-exchange analysis of the product (Fig. 6) showed that in addition to uridine-2′ : 3′ phosphate (11%) two major products were present (24% and 65%) corresponding to uridine benzyl phosphates *a* and *b* respectively (see below). Another, better separation of the two isomers is shown in Fig. 8 (20% and 61% respectively). Treatment of the material with 0·5N-sodium

hydroxide at 37° overnight, and paper chromatography of the product, showed complete conversion into uridylic acid.

Uridine Benzyl Phosphate b.—Uridylic acid (0·5 g. of the crystalline *b*-isomer) was dissolved in dimethylformamide (5 c.c.) and treated dropwise with phenyldiazomethane (from 1 g. of benzaldehyde hydrazone) during 3 min. Ether was added to precipitate the product which was then shaken with chloroform, water, and barium carbonate. The aqueous layer was shaken with more chloroform, treated with charcoal, and evaporated under reduced pressure. The product was dissolved in water, and the solution filtered and freeze-dried. This crude barium salt (0·46 g.) was dissolved in water and converted into the free acid by passage through a column of Amberlite IRC-50 resin (hydrogen form). The product was dissolved in the *iso*propanol–ammonia–water solvent (10 c.c.), containing added water to permit dissolution, and applied to a column (42 × 3·5 cm.) of cellulose powder (160 g. of 80-mesh). The column was developed with the *iso*propanol–ammonia–water and the fractions containing the product collected and evaporated. The residue was dissolved in water, ammonium ions were removed by passage through a column of Dowex-50 resin, and the eluate was freeze-dried. *Uridine benzyl phosphate* b was obtained as a fine hygroscopic powder (0·24 g.) (Found, in material dried at 60°/10^{-3} mm.: C, 45·6; H, 3·9; N, 7·3; P, 7·8. $C_{16}H_{19}O_9N_2P$ requires: C, 46·3; H, 4·6; N, 6·8; P, 7·5%).

A concentrated solution of the material, when set aside overnight at room temperature, was almost completely hydrolysed, under its own acidity, to uridylic acid. A small amount of uridine-2′ : 3′ phosphate was also present.

Hydrogenation of the above benzyl ester (3·7 mg. of the barium salt) in water (0·2 c.c.) over palladium oxide for 15 hr. yielded a solution which was analysed on the ion-exchange column. Only one main product was observed, corresponding to uridylic acid *b* (peak at fraction 69; optical density ratio, 0·32). Uridine-2′ : 3′ phosphate was present in traces (peak at fraction 30).

Action of Ribonuclease on Esters of the Mononucleotides.—Crystalline pancreatic ribonuclease (Armour) was used throughout. Ribonuclease hydrolyses were generally carried out with enzyme concentrations of 0·03 mg. per mg. of substrate in 0·1—0·2 c.c. of water at 37°. The pH was adjusted to *ca.* 8·3 before incubation by the addition of dilute ammonia solution. Buffers were not used, as this facilitated the analysis of the solutions. The materials studied were not affected by the slight changes of pH involved and were unchanged in control experiments in which they were incubated at the same pH but without enzyme. The activity of the enzyme was checked in each set of experiments by including a tube containing uridine-2′ : 3′ phosphate as substrate.

(*a*) *Cytidine derivatives.* The crude barium cytidine benzyl phosphates *a* and *b* (1·1 mg.) were treated as described above with ribonuclease (0·06 mg.) in water (0·4 c.c.). Drops were removed after 1, 2, and 4 hr. at 21° and after incubation overnight at 37°, and applied to paper chromatograms. The benzyl ester spot decreased but did not disappear. The spot corresponding to cyclic phosphate remained of constant intensity (up to 4 hr.) but had disappeared after overnight incubation. The amount of mononucleotide, only a trace at the beginning, increased with time.

The solution of ribonuclease-treated material (3·4 mg.) was analysed on the ion-exchange column. The analysis diagram (Fig. 2) showed that the component corresponding to cytidine benzyl phosphate *b* had disappeared and was replaced by another corresponding to cytidylic acid *b* (peak at fraction 28 with optical density ratio 2·04). Cytidine benzyl phosphate *a* (peak at fraction 45) was unaffected. Fig. 1 is an ion-exchange analysis diagram of untreated material (3·4 mg.).

Cytidine benzyl phosphate *b* (1·5 mg.) gave the ion-exchange diagram shown in Fig. 3. Treatment of this material (1·5 mg.) with ribonuclease (0·06 mg.), and paper chromatography of the solution showed that considerable amounts of cytidine-2′ : 3′ phosphate were present in the solution after 20 min. at room temperature and that after 15 hr. at 37° complete conversion into cytidylic acid had occurred. Analysis of this solution on the ion-exchange column showed that only cytidylic acid *b* was present (peak at fraction 27; optical density ratio 2·02).

Cytidine benzyl phosphate *a* (1·9 mg.) was treated in the usual way with ribonuclease (0·06 mg.). Paper chromatography showed that it was completely unaffected, even after 2 weeks.

Cytidine methyl phosphate (1·0 mg.), when treated with ribonuclease (0·03 mg.), was converted into cytidylic acid (presumably the *b* isomer). Paper chromatography showed that a small amount of the material having the same R_P value as the original ester was unaffected by

the enzyme, even after several days. This was due, undoubtedly, to a slight contamination of the crystalline *b* ester by cytidine methyl phosphate *a*.

(*b*) *Uridine derivatives.* The mixture of barium uridine benzyl phosphates *a* and *b* (2·0 mg.) was treated with ribonuclease (0·06 mg.) as in the case of the cytidine derivatives. Paper chromatography showed the presence of uridine-2′ : 3′ phosphate after 10, 30, and 90 min. but this disappeared after incubation at 37° overnight. Mononucleotide increased in amount during the hydrolysis. A comparison between ion-exchange diagrams of untreated (Fig. 6) and ribonuclease-treated material (6·0 mg.) (Fig. 7) showed that the benzyl ester, present in larger amount (*ca.* 65%), was converted into uridylic acid *b* (peak at 74; optical density ratio 0·33). The unchanged ester (*ca.* 24%) was shown, as follows, to be uridine benzyl phosphate *a*.

The barium salt of the mixed esters (18·2 mg.) was treated exhaustively with ribonuclease and then the solution was freeze-dried. After its dissolution in a small amount of water, the solution was applied to a paper strip (16-cm. line), and the chromatogram developed with the *iso*propyl alcohol–ammonia–water solvent. The strip containing the unchanged ester was eluted with water (0·2 c.c.), and the eluate hydrogenated over a mixed palladium oxide–palladium-charcoal catalyst for 24 hr. The solution was analysed on the ion-exchange column. The diagram showed only one component, corresponding to uridylic acid *a* in the position of the peak and the optical density over the peak (0·26). It followed that uridine benzyl phosphate *b* was alone hydrolysed by ribonuclease.

Barium uridine benzyl phosphate *b* (2·0 mg.) was treated with ribonuclease (0·06 mg.). After 12 hr. complete conversion into uridylic acid was shown by paper chromatography.

(*c*) *Other compounds.* Uridine-5′ (benzyl phosphate), adenosine-5′ (benzyl phosphate), and the mixed barium salts of adenosine benzyl phosphate *a* and *b* were each treated with ribonuclease in the usual way. In no case did paper chromatography disclose any action of the enzyme on these substances. In addition to the *iso*propyl alcohol–ammonia–water solvent, the butanol–acetic acid–water and disodium hydrogen phosphate–*iso*amyl alcohol solvents were used with the adenosine derivatives since these solvents effect separation of the *a* and *b* isomers of both the adenylic acids and their benzyl esters (Brown and Todd, Part IX, *loc. cit.*).

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417. 6-*Aminosalicylic Acid: The Hydrolysis of 2-Carboxytrinitrodiphenyl Ethers.*

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Hydrolysis of 2-chloro-6-nitrobenzoic acid with aqueous potassium carbonate at 175° gave 6-nitrosalicylic acid in unsatisfactory yield. Condensation of 2-chloro-6-nitrobenzoic acid with phenol and nitration of the product yielded 2-carboxy-3 : 2′ : 4′-trinitrodiphenyl ether; this was hydrolysed by dilute alkali to 6-nitrosalicylic acid and 2 : 4-dinitrophenol. Yields were high at all stages.

The hydrolytic scission of 2-carboxydiphenyl ethers bearing 2′- and 4′-nitro-groups appears to be general.

Much has been published on the use of 4-aminosalicylic acid against human tuberculosis. Since its introduction by Lehman (*Lancet*, 1946, **250**, 15). The activities of 3- and 5-aminosalicylic acids against *M. tuberculosis in vitro* are far lower than that of the 4-isomer (Hurt and Hurni, *Helv. Chim. Acta*, 1949, **32**, 378) but there is no record of the activity of 6-aminosalicylic acid. Justoni (*Farm. sci. e tec., Pavia*, 1950, **5**, 165; *Chem. Abs.*, 1950, 7807) prepared the compound but did not report experimental details or the synthetical route.

The necessary intermediate, 6-nitrosalicylic acid, was isolated in unspecified yield by Mehta and Ayyar (*J. Univ. Bombay*, 1939, **8**, Part 3, 176) as an oxidation product of 5-nitrobenzo-1 : 3-dioxen (cf. Buehler, Deeble, and Evans, *J. Org. Chem.*, 1941, **6**, 216). This

method was found to have little preparative value and attention was turned to the easily accessible 2-chloro-6-nitrobenzoic acid. Attempted hydrolysis of this by aqueous potassium carbonate at 150° in the presence of a copper catalyst was unsuccessful. At 175°, however, 6-nitrosalicylic acid was obtained in *ca.* 10% yield together with considerable quantities of *m*-chloronitrobenzene and unchanged 2-chloro-6-nitrobenzoic acid. The stability of the halogen in 2-chloro-6-nitrobenzoic acid towards potassium carbonate is remarkable in view of the rapid hydrolysis of the 3-, 4-, and 5-nitro-isomers by this reagent (Goldberg, *J.*, 1952, 4368).

Fission of a diphenyl ether group in nitroxanthones by alkali (Meisenheimer, *J. pr. Chem.*, 1928, **119**, 315) or piperidine (Le Fèvre, *J.*, 1928, 3249) and in polynitrodiphenyl ethers by nucleophilic reagents (G.P. 620,761; Borrows *et al.*, *J.*, 1949, 5190) suggested that polynitrated 2-carboxy-diphenyl ethers would be amenable to hydrolytic cleavage to nitrosalicylic acids and nitrophenols: 2'- and 4'-nitro-groups should create a sufficiently strong electron defect at $C_{(1')}$. Condensation of 2-chloro-6-nitrobenzoic acid with phenol and treatment of the 2-carboxy-3-nitrodiphenyl ether thus produced with nitric acid gave 2-carboxy-3 : 2' : 4'-trinitrodiphenyl ether, which with aqueous alkali at 100° disrupted into 6-nitrosalicylic acid and 2 : 4-dinitrophenol, which were easily separated; yields at all stages were high.

Similarly, nitration of 2-carboxy-5- and -6-nitrodiphenyl ether gave the 5 : 2' : 4'- and 6 : 2' : 4'-trinitro-ethers, which were hydrolysed by alkali to 4- and 3-nitrosalicylic acid respectively. Treatment of 2-carboxydiphenyl ether with nitric acid under the same conditions afforded the 4 : 2' : 4'-trinitro-ether and thence 5-nitrosalicylic acid and 2 : 4-dinitrophenol.

Hydrogenation of 6-nitrosalicylic acid over palladium–charcoal gave 6-aminosalicylic acid.

The annexed Table shows the minimum concentration (mg./l.) of the compounds which completely inhibit growth of *M. tuberculosis* H37 during an incubation period of 3 weeks.

Acid	Veal broth (*a*)	Veal broth 5% Serum	D'Arcy Hart (*b*)	D'Arcy Hart 5% Serum
3-Aminosalicylic	125	250	125	250
4-Aminosalicylic	0·5	0·5	0·5	0·5
5-Aminosalicylic	>250	>250	>250	>250
6-Aminosalicylic	125	125	250	250

(*a*) Floating pellicle growth (Goldberg, Jefferies, Turner, and Besly, *J. Pharm. Pharmacol.*, 1946, **19**, 483). (*b*) Dispersed growth; inoculum 1 million organisms per c.c. of medium (Dubos and Davies, *J. Exp. Med.*, 1946, **83**, 409; D'Arcy Hart, *Nature*, 1947, **160**, 94).

Experimental

Equivalent weights of the 2-carboxytrinitrodiphenyl ethers were determined by titration with aqueous potassium hydroxide at 0° in order to avoid hydrolysis.

2-Carboxy-3-nitrodiphenyl Ether.—2-Chloro-6-nitrobenzoic acid (50 g.) and copper bronze (1 g.) were added to a solution of potassium hydroxide (30 g.) in phenol (250 g.) and the mixture stirred at 150° (internal) for 6 hr. The phenol was distilled off in a current of steam, and the residual aqueous solution filtered (charcoal) and acidified to pH 3 with 10N-hydrochloric acid. The precipitate was dissolved in boiling water (600 c.c.) containing potassium carbonate (30 g.), and the solution evaporated to small volume and chilled. The potassium salt, on collection and conversion into the free acid, gave *2-carboxy-3-nitrodiphenyl ether* (30 g.; m. p. 158°) as a light brown powder. A sample crystallised from 90% alcohol in colourless needles, m. p. 162° (Found: equiv., 257; N, 5·5%. $C_{13}H_9O_5N$ requires equiv., 259; N, 5·4%). The acid is appreciably soluble in hot water.

2-Carboxy-3 : 2' : 4'-trinitrodiphenyl Ether.—2-Carboxy-3-nitrodiphenyl ether (21 g.) was added during ½ hr. to nitric acid (200 c.c.; *d* 1·5) stirred at 0°. After a further 2 hr. at 0—5° the solution was poured on ice (500 g.); the precipitate (27 g.), crystallised from alcohol, gave *2-carboxy-3 : 2' : 4'-trinitrodiphenyl ether* (18 g.) in fine pale yellow needles, m. p. 194° (Found: equiv., 346; N, 12·1%. $C_{13}H_7O_9N_3$ requires equiv., 349; N, 12·0%).

6-Nitrosalicylic Acid.—A solution of the foregoing acid (35 g.) in 2·5N-sodium hydroxide (250 c.c.) was heated on the steam-bath for 1 hr., cooled, and acidified to pH 4·5 with hydro-

chloric acid. The precipitate of 2 : 4-dinitrophenol, m. p. and mixed m. p. 114° (Found : N, 14·8. Calc. for $C_6H_4O_5N_2$: N, 15·2%), was removed and the filtrate acidified to pH 2 with 10N-hydrochloric acid and extracted with ether (4 × 250 c.c.). Removal of the ether gave 6-nitrosalicylic acid (10 g.), pale yellow needles, m. p. 172° (from toluene) [Found : equiv., 183; *M* (Rast), 180; C, 45·8; H, 2·8; N, 7·7%. Calc. for $C_7H_5O_5N$: equiv. = *M*, 183; C, 45·8; H, 2·7; N, 7·7%). In contrast to 4- and 5-nitrosalicylic acids, the 6-isomer is very soluble in cold water and in ether.

6-*Aminosalicylic Acid.*—The foregoing acid (10 g.), water (120 c.c.) and 5N-hydrochloric acid (10 c.c.) were shaken with palladium chloride (0·6 g.) and charcoal (3 g.) in hydrogen at 15°/760 mm. (uptake, 3800 c.c. at N.T.P.; $3H_2$, 3680 c.c.). The filtered solution was evaporated at reduced pressure to *ca.* 70 c.c. and chilled. The colourless crystalline precipitate of *6-aminosalicylic acid hydrochloride* (6·6 g.), m. p. 216° (decomp.), was collected (Found : N, 8·2; Cl, 18·8. $C_7H_8O_3NCl$ requires N, 7·4; Cl, 18·7%); evaporation of the filtrate to dryness yielded a residue (5 g.), m. p. 178°. This, together with the first precipitate, was dissolved in 5% aqueous sodium hydrogen carbonate (120 c.c.), and the filtered solution acidified to pH 4 with acetic acid; plates of 6-aminosalicylic acid (4·2 g.), m. p. 148°, separated which were collected and dried at 20°/2 mm. (Found : equiv., 154; N, 9·2%. Calc. for $C_7H_7O_3N$: equiv., 153; N, 9·2%).

2-*Carboxy*-5 : 2′ : 4′-*trinitrodiphenyl Ether.*—2-Carboxy-5-nitrodiphenyl ether (11 g.; Goldberg and Walker, *J.*, 1953, 1348) was added during ¼ hr. to nitric acid (100 c.c.; *d* 1·5) stirred at 5—10°. The solution was kept for a further 2¼ hr. at 10° and then poured on ice (600 g.). The precipitate (15 g.) was collected, washed with water, dried *in vacuo*, and dissolved in 150 c.c. of toluene–dioxan (3 : 1), and the hot filtered solution diluted with 90 c.c. of ligroin (b. p. 80—100°). 2-*Carboxy*-5 : 2′ : 4′-*trinitrodiphenyl ether* separated in colourless hydrated tablets; these (12·7 g.), on drying at 90°, gave the anhydrous acid (11·5 g.), m. p. 188—190° (Found : equiv., 348; N, 12·1%. $C_{13}H_7O_9N_3$ requires equiv., 349; N, 12·0%).

4-*Nitrosalicylic Acid.*—A solution of the foregoing crude acid (10·0 g.) and potassium carbonate (250 g.) in water (150 c.c.) was heated on the water-bath for 6 hr. A precipitate obtained at pH 5 consisted of 2 : 4-dinitrophenol and its potassium salt, giving on recrystallisation from acidic aqueous alcohol, 2 : 4-dinitrophenol (4·0 g.), m. p. and mixed m. p. 116—118°. Adjustment to pH 2 gave 4-nitrosalicylic acid (4·9 g.), lemon-yellow needles (from aqueous alcohol), m. p. and mixed m. p. 236° (Found : equiv., 183; N, 7·8%).

2-*Carboxy*-6 : 2′ : 4′-*trinitrodiphenyl Ether.*—Nitration of 2-carboxy-6-nitrodiphenyl ether (20 g.; Goldberg and Walker, *loc. cit.*) as for the 3-nitro-isomer, gave the 6 : 2′ : 4′-*trinitro-ether* (21 g.) in pale yellow plates (from ethanol), m. p. 176° (Found : equiv., 340; N, 12·1%).

3-*Nitrosalicylic Acid.*—A solution of the foregoing acid (10 g.) in 5% aqueous potassium carbonate (500 c.c.) was evaporated on the water-bath to incipient crystallisation. Treatment as previously described gave 2 : 4-dinitrophenol (4·0 g.; m. p. 111°) and 3-nitrosalicylic acid (4·0 g.), needles (from water), m. p. and mixed m. p. 145° (Found : equiv., 184; N, 7·5%).

2-*Carboxy*-4 : 2′ : 4′-*trinitrodiphenyl Ether.*—2-Carboxydiphenyl ether (21·4 g.) was added during 1 hr. to nitric acid (200 c.c.; *d* 1·5) stirred at 0°. After a further 2 hr. at 5—10° the solution was poured on ice (1000 g.) and the 4 : 2′ : 4′-*trinitro-ether* (28 g.; m. p. 155°) collected, washed and, dried at 60°. A sample crystallised from dilute alcohol in pale yellow needles with the same m. p. (Found : equiv., 346; N, 12·1%).

5-*Nitrosalicylic Acid.*—A solution of the foregoing acid (20 g.) in N-sodium hydroxide (500 c.c.), heated on the water-bath for 2 hr., gave 2 : 4-dinitrophenol (9 g.; m. p. 110°) at pH 5 and, at pH 2, 5-nitrosalicylic acid (7·5 g.), needles, m. p. and mixed m. p. 232° (Found : equiv., 186; N, 7·8%).

Hydrolysis of 2-*Chloro*-6-*nitrobenzoic Acid.*—A solution of 2-chloro-6-nitrobenzoic acid (20·2 g.) in water (500 c.c.) and potassium carbonate (20·2 g.) was heated with copper bronze (1 g.) and cuprous iodide (1 g.) in an autoclave for 7 hr. at 175° (internal); the pressure was 110 lb./sq. in. After chilling, the catalyst and impure *m*-chloronitrobenzene (*ca.* 6 g.) were filtered off and the solution extracted with ether. The aqueous layer was evaporated to *ca.* 300 c.c., strongly acidified with 5N-sulphuric acid, and set aside overnight. The precipitate of unchanged 2-chloro-6-nitrobenzoic acid (5·5 g.; m. p. and mixed m. p. 160—162°) was removed and the filtrate extracted with ether. Evaporation of the ethereal solution gave 6·5 g. of very impure 6-nitrosalicylic acid; this was dissolved in dilute potassium carbonate, the solution evaporated to very small volume and chilled and the precipitated potassium salt collected (filtrate F). The precipitate was dissolved in a small amount of water, the solution acidified, and the precipitate (3 g.; m. p. 160°) of 2-chloro-6-nitrobenzoic acid removed. The filtrate was combined with filtrate F, acidified, and extracted with ether; evaporation of the

ether yielded 1·6 g. of 6-nitrosalicylic acid, m. p. and mixed m. p. 166—168° (Found: equiv., 186).

When the above experiment was carried out at 150—155° for 6½ hr. 2-chloro-6-nitrobenzoic acid (15 g.) was recovered.

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418. *Hyperconjugation. Part I. Conjugation and Hyperconjugation Energies.*

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By improved calculations for a series of methyl-benzenes and -ethylenes the hyperconjugation energy per methyl group has been found to be constant.

A detailed comparison of the empirical and theoretically computed delocalisation energies of benzene and butadiene yields a value of approximately −74 kcal. for β_0, the resonance integral (including overlap) for the C=C bond distance of 1·39 Å.

The strengthening of single and double bonds by hyperconjugation is found to be less than previous estimates, the total contribution of third-order conjugation to the bond energies of both single and double bonds being only about 1·6 kcal.

THE conjugation of alkyl groups with multiple bonds is known as hyperconjugation. Methyl groups, because of their symmetry, are more effective for this purpose than higher alkyl groups. However, since alkyl groups are saturated, the degree of delocalisation is much smaller than that which occurs in ordinary conjugated systems. Nevertheless, the occurrence of hyperconjugation in certain molecules is revealed by small but definite changes in the static and dynamic characteristics of such molecules. Thus progressive alkylation of a double bond in an unsaturated molecule results not only in displacement of its ultra-violet absorption spectrum towards longer wave-lengths but also in progressive stability of the molecule, as shown by diminution of its heat of hydrogenation. In reaction kinetics the usual inductive-effect order of alkyl groups is inverted in strongly electron-demanding reactions. (For a comprehensive review see Crawford, *Quart. Reviews*, 1949, **3**, 226.)

In a study of the phenomenon, Mulliken, Rieke, and Brown (*J. Amer. Chem. Soc.*, 1941, **63**, 41) computed the hyperconjugation energies and bond orders for a number of methylated compounds. Their work took cognisance of the fact that the resonance integral β varies with bond length and they determined its mode of variation from empirical evidence. In like manner they deduced an empirical resonance integral for hyperconjugated C–H bonds but assumed the Coulomb integral for H_3 in CH_3 to be the same as for C in C=C. On this basis they derived a value for β of about 45 kcal. per mole for a C=C bond-length of 1·33 Å and showed that hyperconjugation strengthens ordinary single and double bonds by about 2·5 and 5·5 kcal. per mole, respectively.

In a similar way Roberts and Skinner (*Trans. Faraday Soc.*, 1949, **45**, 339) calculated the hyperconjugation energies in certain hydrocarbon molecules and radicals. They determined the dependence of the resonance integral on C–C distance but neglected the non-zero values of the orthogonality integrals.

It is the purpose of the present work to improve and to extend the calculations referred to above. This we do by accepting the main feature of Mulliken's model in which the three hydrogen atoms function as a single pseudo-atom with one π-electron. The improvements consist (i) in regarding the pseudo-atom H_3 as a hetero-atom with an electronegativity different from that of carbon and (ii) in allowing for the variation of the resonance integral with distance by assuming it to be proportional to the overlap integral. In this way it will be shown that a value for β can be deduced which is close to the

spectroscopic value. The delocalisation energies for a series of methyl-benzenes and -ethylenes are reported here.

Method of Calculation.—The method of calculation is that of molecular orbitals with inclusion of the overlap integral S between adjacent atomic orbitals. It will be illustrated for the case of toluene, the numbering shown in the annexed figure being used for convenience. Associated with the pseudo-atom H_3 is a π orbital formed by grouping of the three hydrogen atom 1s atomic orbitals. Consequently the molecule has eight π electrons, each of which is supposed to move in a molecular orbital ψ embracing all the nuclei and represented by a linear combination of the π orbitals ϕ_i so that

$$\psi = \sum_{i=1}^{8} c_i \phi_i$$

The energies of the electron levels are given by the roots of the secular equation $|H_{ij} - ES_{ij}| = 0$ in which

$$E = \int \psi^* H \psi \mathrm{d}\tau;\ H_{ii} = \int \phi_i^* H \phi_i \mathrm{d}\tau = \alpha_i;\ H_{ij} = \int \phi_i H \phi_j \mathrm{d}\tau = \gamma = H_{ji};$$
$$S_{ij} = \int \phi_i \phi_j \mathrm{d}\tau;\ S_{ii} = \int \phi_i \phi_i \mathrm{d}\tau = 1;\ \text{and } \beta = \gamma - S\alpha$$

In these definitions we have preserved the original significance of β and γ to facilitate comparison with Mulliken's work. Care is needed since it frequently happens now that β and γ are interchanged. All the ϕ_i are purely real functions.

In order to solve the secular equations for E and the coefficients c_i, values must be assumed for S and γ (and hence for β). These latter quantities are functions of the lengths of the individual bonds and are therefore different from S_0 and γ_0 (and β_0), the corresponding values for unsubstituted benzene. The assumption (Wheland, *J. Amer. Chem. Soc.*, 1941, **63**, 2025) that γ is proportional to S permits parameters to be defined such that

$$\rho_{12} = \gamma_{12}/\gamma_0 = S_{12}/S_0;\ \rho_{23} = \gamma_{23}/\gamma_0 = S_{23}/S_0.$$

The $2p\pi$ overlap integrals which are required are easily evaluated for various lengths of bond, Slater wave functions being used and a value of 3·25 for Z, the effective nuclear charge of carbon. The results, which show a surprisingly large variation between single and triple bonds, are recorded in Table 1. They agree excellently with values interpolated from the comprehensive collection of integrals recently published by Mulliken, Rieke, Orloff, and Orloff (*J. Chem. Phys.*, 1949, **17**, 1248).

A value must also be assumed for the Coulomb term of the pseudo-atom H_3. In order to ensure π-electron migration from the methyl group into the ring, as required by the *op* directing property of the substituent in electrophilic reactions, this was taken to be a more electropositive atom than carbon, and the corresponding diagonal element H_{11} in the secular equation set equal to $\alpha + \delta_1\beta_0$ with $\delta_1 = -0{\cdot}5$. This electropositivity of H_3 was shared somewhat with the adjacent carbon atom whose Coulomb term was taken as $\alpha + \delta_2\beta_0$, with $\delta_2 = -0{\cdot}1$. There is some arbitrariness in this choice of parameters. Since, however, they are chosen to reproduce the dipole moment of toluene, assuming it to be a resonance moment, they are unlikely to be very seriously wrong. If it is agreed that

TABLE 1. *Variation of* S *with bond length.*

r(C–C), Å	1·20	1·33	1·35	1·39	1·46	1·54	C–H_3
S	0·336	0·273	0·264	0·247	0·219	0·191	0·64

δ_2 must be considerably smaller than δ_1, then values similar to those which we have selected would be almost inevitable.

Now the presence of a substituent in an aromatic molecule induces a change in the electronic structure of the molecule. This effect is usually regarded as manifesting itself in two ways (Coulson, *Proc. Phys. Soc.*, 1952, **65**, *A*, 933; Dewar, *J. Amer. Chem. Soc.*, 1952, **74**, 3341; Longuet-Higgins and Sowden, *J.*, 1952, 1404): (i) If the substituent X possesses π electrons these will interact with or perturb the π electrons of the aromatic molecule. As a result the effective length of the conjugation path is increased. This is the conjugative effect and it results in charge shifts, and changes in π electron energies, etc.

It is taken into account by considering the appropriate number of π electrons in molecular orbitals extending over the whole nuclear framework. (ii) Since in general the electronegativity of the substituent X will be different from that of the carbon centre to which it is attached, a polarised C–X σ bond results. This in turn polarises adjacent bonds in the aromatic molecule and so the effect is transmitted. This is the inductive effect. It diminishes in magnitude with distance from the C–X bond and can be taken into account by assigning a value to H_{ii} for the carbon centre to which the substituent is attached different from α_c. As a first approximation, this latter effect is ignored in the present study except insofar as it is partly included in the parameter δ_2, the hyperconjugative effect chiefly being dealt with.

Rounded values for ρ, *viz.* $\rho_{12} = 2{\cdot}5$ and $\rho_{23} = 0{\cdot}7$, were chosen and the determinantal equation was solved to yield all eight energy values; the most negative of these corresponds to the lowest, *i.e.*, the most stable, molecular orbital. These energies are all of the form $E_j = \alpha + k_j\beta_0$, where the various k_j are found from the secular determinant. The energies are therefore computed in terms of β_0 which is here taken as a standard. Its value will subsequently be determined by comparing computed and empirical conjugation energies in benzene and butadiene which are taken as reference molecules. This procedure is superior to the previous rather troublesome trial-and-error method of determining the variation of β with distance. The four lowest energy values which result being assumed to be each doubly-filled, the total π-electron energy E^{mobile} is found to be

$$E^{\text{mobile}} = 8\alpha + 8{\cdot}6102\beta_0.$$

To obtain the delocalisation energy the total energy E^{loc} of the π-electrons in a localised bond structure must be computed. This is simply

$$\begin{aligned} 2E_{\text{C}\equiv\text{H}_2} + 6E_{\text{C}=\text{C(benzene)}} &= 2(\alpha + 1{\cdot}3613\beta_9) + 6(\alpha + 0{\cdot}8000\beta_0) \\ &= 8\alpha + 7{\cdot}5226\beta_0 \end{aligned}$$

The total delocalisation energy is therefore $1{\cdot}0877\beta_0$. Deducting from this the conjugation energy of benzene, *viz.*, $1{\cdot}0666\beta_0$, we obtain $0{\cdot}0211\beta_0$ as the extra stability of the molecule due to conjugation between the methyl group and the benzene ring. Hyperconjugation energies obtained in this way for several methyl-benzenes and -ethylenes are recorded in Table 2 in units of β_0.

Empirical Conjugation Energies.—For the empirical determination of conjugation energies two methods are available. They are based on the heats of hydrogenation and combustion. Although heats of hydrogenation normally provide the most accurate data

TABLE 2. *Hyperconjugation Energies (H.E.) of Methyl-benzenes and -ethylenes.*

	Computed (in units of β_0)			Empirical (in kcals.)	
Molecule	H.E.	No. of Me groups	H.E. per Me group	H.E. (Δ)	H.E. per Me group
Toluene	0·0211	**1**	0·0211	1·5	1·5
o-Xylene	0·0423	**2**	0·0211	2·54	1·27
m-Xylene	0·0422	**2**	0·0211	2·96	1·48
p-Xylene	0·0422	**2**	0·0211	2·79	**1·39**
Mesitylene	0·0632	**3**	0·0211	4·54	**1·51**
Durene	0·0845	**4**	0·0211	5·66	**1·41**
Propylene	0·0242	**1**	0·0242	1·20	1·20
cis-Butene	0·0485	**2**	0·0242	1·06	0·53
*iso*Butene	0·0477	**2**	0·0239	2·11	1·55
Tetramethyl ethylene	0·0961	**4**	0·0240	3·05	0·76

for the determination of conjugation energies, these are not as extensive as might be desired. Consequently, heats of combustion (National Bureau of Standards, Project 44) which have been determined with greater accuracy have been used for this purpose. It has been shown (Mulliken, Rieke, and Brown, *J. Amer. Chem. Soc.*, 1941, **63**, 41) that the following expression fits with great fidelity the data for non-conjugated hydrocarbons:

$$-\Delta H_{298} = 54{\cdot}625N_{\text{CH}} + 48{\cdot}25N_{\text{CC}} - 1{\cdot}5N_{\text{Me}} + 22{\cdot}18N_{\text{C}=\text{C}} + 56{\cdot}6N_{\text{C}\equiv\text{C}} \quad . \quad (1)$$

Here, N_{CH}, N_{CC}, $N_{\text{C}=\text{C}}$, $N_{\text{C}\equiv\text{C}}$ are the numbers of C–H bonds, C–C bonds, C=C double bonds, C≡C triple bonds, respectively, and N_{Me} is the number of methyl groups. Negative departures Δ from heats of combustion predicted by this equation yielded the figures

recorded in column 5 of Table 2. (The figures for the methylbenzenes were obtained after subtraction from the total conjugation energy of that due to benzene.)

Corrections for Extension and Compression of Bonds and Third-order Conjugation.—The direct comparison of theoretically computed and empirically determined conjugation energies is not a completely fair one for two reasons:

(i) The total energy of a conjugated molecule involves not only the energy of the π electrons, but also the energy of compression and extension of the C–C σ bonds. In the calculation of empirical conjugation energies, therefore, account must be taken of the changes in the lengths of the bonds. The importance of doing this has recently been stressed by several workers (*e.g.*, Lennard-Jones, *Proc. Roy. Soc.*, *A*, 1937, **138**, 280; Mulliken, Rieke, and Brown, *loc. cit.*; Hornig, *J. Amer. Chem. Soc.*, 1950, **72**, 5772; Coulson and Altmann, *Trans. Faraday Soc.*, 1952, **48**, 293). Here the compression and extension energies $C_s(r)$ and $C_d(r)$ were calculated from Morse functions

$$C(r) = D\{\exp[-a(r - r_e)] - 1\}^2$$

in which the exponent a was obtained from the expression

$$a = (k_e/2D)^{\frac{1}{2}}$$

where k_e is the bond force constant and D the bond dissociation energy. The following reasonable values of these parameters were used:

Bond type	D (kcal.)	$10^8 r_e$	$10^5 k_e$, dyne cm.$^{-1}$
C–C	83	1·54	4·5
C=C	141·5	1·33	8·2

and the results obtained set out in Table 3. Small variations from these values of the parameters would not sensibly affect our results.

TABLE 3. *Compression energies (kcal./mole).*

r(C–C), Å ...	1·54	1·52	1·49	1·46	1·43	1·39	1·36	1·33	1·30	1·27	1·24	1·22	1·20
$C_s(r)$	0·00	0·13	0·90	2·43	4·98	9·98	15·27	23·09	30·78	41·61	54·72	65·15	83·17
$C_d(r)$	17·42	14·81	11·11	7·78	4·88	1·90	0·50	0·00	0·56	2·41	5·80	9·01	13·10

(ii) Since the single bond in ethane is strengthened by third-order conjugation, the ideal single bond is one which is slightly longer (Mulliken, Rieke, and Brown, *loc. cit.*) than that found in ethane. Similarly the ideal double bond is one which is weaker and slightly longer than that of ethylene. In computing the total conjugation energy therefore in a system containing single and double bonds, allowance must be made for the strengthening of these bonds compared with the ideal standards. For example, in benzene where all the bonds are of equal length, this additional strengthening (R_y) is simply six times that per single bond calculated for the length obtaining in benzene. The total conjugation energy computed theoretically is therefore given by

$$R = R_x + R_y \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where R_x is the ordinary or first-order conjugation.

Here the third-order conjugation energies for both ethane and ethylene were obtained on the basis of the same secular equations, it being assumed that $\rho_{C\equiv H_3}$ is the same as $\rho_{C=H_2}$. When overlap is included, the calculation of third-order conjugation energy is straightforward. It may readily be shown to be

$$2\beta_0\left\{\frac{2S_0\rho_{12}^2 + (\rho_{23}^2 + 4\rho_{12}^2)^{\frac{1}{2}}}{1 + S_0^2\rho_{12}^2 + S_0(\rho_{23}^2 + 4\rho_{12}^2)^{\frac{1}{2}}} - \frac{2\rho_{12}}{1 + S_0\rho_{12}}\right\}$$

per dimension where ρ_{12} and ρ_{23} refer to the C≡H$_3$ and C=C bonds, respectively. This expression being used, values of R_y per bond were computed for various bond lengths. The results obtained are set out in Table 4.

Now it has been shown (Mulliken, Rieke, and Brown, *loc. cit.*) that

$$R = \Delta + C + 2\delta_{1\cdot54}N_{C-C} + \delta_{1\cdot33}N_{C=C} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where C is the energy correction for changes in bond length due to conjugation, and δ is the hyperconjugation energy per bond per dimension for bond lengths of 1·54 and 1·33 Å, respectively.

Comparison of expressions (2) and (3) shows that

$$\Delta + C = R_x + R_y - 2\delta_{1\cdot54}N_{C-C} - \delta_{1\cdot33}N_{C=C} \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Table 5 (drawn up in a similar manner to Table 6 of the paper by Mulliken, Rieke, and Brown) contains the theoretically computed quantities occurring on the right side of equation (4). In addition, for the reference molecules benzene and butadiene, the theoretically computed $\Delta + C$ (in column 7) is compared with the empirical value (column 10).

Discussion.—Table 2 shows clearly that the hyperconjugation energy per methyl group is constant in both series of compounds. However, the computed magnitude of this quantity is slightly greater in the ethylene than in the benzene series. This is accounted

TABLE 4. *Third-order conjugation energies: $\delta(r)$ values.*

r(C–C), Å	1·54	1·46	1·39	1·35	1·33
$\delta(r)$, in units of β_0	0·0092	0·0122	0·0154	0·0176	0·0187

for by the fact that the magnitude of the delocalisation energy is sensitive to the value of ρ which will be different for the two series of compounds because of the slightly different bond lengths.

The almost exact constancy of the hyperconjugation energy per methyl group is parallel to a similar additivity relation for charge migrations caused by hyperconjugation, reported in the following paper. This provides a partial justification for treating the whole effect as a perturbation one and considering only first-order perturbation theory. Such an approach to the problem has sometimes been made in the past, though without the detailed support provided by our present calculations.

There are two values of the delocalisation energy of *cis*- and *trans*-butene because in expression (1) no distinction is made between isomeric compounds. Since, however, the thermal data for these compounds do differ, this is reflected in differences in the delocalisation energies.

TABLE 5. *Conjugation energies.*

		Theoretical, in units of $\lvert\beta_0\rvert$					Empirical, in kcals.			
Molecule	r(C–C), Å	R_x	R_y	R	Deduction *	$\Delta + C$	Δ	C	$\Delta + C$	β_0
Benzene	1·39	1·0666	0·0924	1·1590	0·1113	1·0477	39·46	35·49	74·95	−71·6
Toluene	1·39	1·0877	0·1016	1·1893	0·1297	1·0596	—	—	—	—
	1·54									
o-Xylene	1·39	1·1089	0·1108	1·2197	0·1481	1·0716	—	—	—	—
	1·54									
m-Xylene	1·39	1·1088	0·1108	1·2196	0·1481	1·0715	—	—	—	—
	1·54									
p-Xylene	1·39	1·1088	0·1108	1·2196	0·1481	1·0715	—	—	—	—
	1·54									
Mesitylene	1·39	1·1298	0·1200	1·2498	0·1665	1·0833	—	—	—	—
	1·54									
Durene	1·39	1·1511	0·1292	1·2803	0·1849	1·0954	—	—	—	—
	1·54									
Propylene	1·33	0·0242	0·0279	0·0521	0·0371	0·0150	—	—	—	—
	1·54									
cis-Butene	1·33	0·0485	0·0371	0·0856	0·0555	0·0301	—	—	—	—
	1·54									
Tetramethyl-	1·33	0·0961	0·0555	0·1516	0·0923	0·0593	—	—	—	—
ethylene	1·54									
Butadiene	1·35	0·1253	0·0474	0·1727	0·0558	0·1169	5·45	3·43	8·88	−75·9
	1·46									

* $2\delta_{1\cdot54}N_{C-C} + \delta_{1\cdot33}N_{C=C}$.

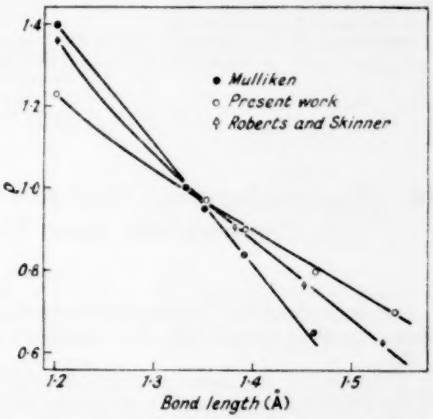
The values obtained for $\lvert\beta_0\rvert$ by comparison of the theoretical and empirical conjugation energies (see Table 5, columns 7, 10, and 11) of benzene and butadiene are 71·6 and 75·9 kcal., respectively. An average value for $\lvert\beta_0\rvert$ of 73·8 kcal. being used, the third-order conjugation energies computed here are set out in Table 6 together with those of Mulliken, Rieke, and Brown (M.R.B.), and Roberts and Skinner (R.S.).

The magnitudes of the third-order conjugation energies presented here are appreciably less than the M.R.B. and R.S. values. The large difference between the results contained

in the third and the fourth rows of the Table is no doubt due to the fact that, although Roberts and Skinner determined the variation of β with distance, the overlap integral was neglected. Although Wheland (*J. Amer. Chem. Soc.*, 1941, **63**, 2025) concluded that for unsubstituted hydrocarbons its neglect is not a source of error, Skinner himself points out that Wheland's calculations were not made from the starting point of a dependence of β on distance.

A further reason for the discrepancy between the figures in rows two and three and those in the fourth row is ascribed to the different rates of variation of β with distance in the three sets of calculations. This is shown clearly in the Figure in which the variation of ρ with bond length is plotted. It is at once evident that the variation of β with distance in the present work is much less rapid than that previously obtained.

Although there is no means of directly determining third-order conjugation energies, the values obtained in the present study would seem to be more reasonable than the results of the two previous computations. Even allowing for the fact of a more intense conjugation across a shorter bond, a third-order conjugation energy of 5—7 kcal. in ethylene seems rather large. If it were indeed so, this would mean that the third-order conjugation



Variation of C–C resonance integral $\beta(\rho = \beta/\beta_0)$ as a function of bond length.

in ethylene is comparable with ordinary conjugation between the two double bonds, as in butadiene. This is hardly likely.

The value of β_0 (= −73·8 kcal./mole) which we have obtained is larger than the value to be expected without the inclusion of overlap integrals, and a little larger than that recently obtained by Mulliken (*J. Chem. Phys.*, 1949, **46**, 497), but it lies in the region which is now considered plausible. In particular it corresponds closely with the " spectroscopic " value, chosen to fit the ultra-violet absorption of ethylene or benzene. It must be

TABLE 6. *Third-order conjugation energies in kcal./mole (per dimension of pseudo π-electrons).*

r(C–C), Å	1·55	1·53	1·45	1·39	1·34
M.R.B.	—	1·35	2·37	3·93	5·54
R.S.	2·50	2·76	4·20	5·6	7·08
Present work	0·78	—	0·90	1·14	1·58

considered reasonably satisfactory that although our value of β_0 is greater than that of Mulliken, Rieke, and Brown, our third-order conjugation energies are smaller.

In conclusion it is important that the uncertain nature of some of our assumptions should be stressed. Three of these appear to us to be of greater significance than the rest. The first—and most important—is the chief point of the model, whereby an H_3 group is represented by a single pseudo-atom with one π-electron. This carries with it the assumption that the carbon atom also has π-electron orbitals (to permit the extended conjugation). This suggests strongly that this carbon atom should be regarded as

digonally hybridised—a conclusion which is at variance with more conventional and simple descriptions of normal saturated carbon compounds. The second assumption is that when the system is treated as a π-electron system, there is no π–σ resonance. Recent work (Altmann, *Proc. Roy. Soc., A*, 1952, **210**, 327, 343) suggests that even in ethylene there may be some resonance interaction between π and σ bonds. It might be expected that this would be more important still in the conjugation of methyl groups with unsaturated and aromatic systems. Finally—though this is partly included in our second assumption—the hypothesis that one single configurational wave-function is adequate to describe the molecule would appear unjustified in view of the work of Coulson, Craig, and Jacobs (*Proc. Roy. Soc., A*, 1950, **202**, 498; 1951, **206**, 287, 297), on configurational interaction.

These three difficulties are in addition to those associated with the method of molecular orbitals itself, and which are well known. Notwithstanding the semi-empirical character which these difficulties force upon our calculations, we believe that they do provide further support for the general picture of the phenomenon of hyperconjugation as put forward by Mulliken.

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419. *Hyperconjugation. Part II.* Charge Distributions in Propylene and Some Methylbenzenes.*

By V. A. CRAWFORD.

The π-electron densities in propylene and some polymethylbenzenes have been computed theoretically and correlated with their substitutional reactivity.

The effect of successive methyl substituents on the charge distribution in the benzene ring is found to be strictly additive.

Attention is drawn to the need for caution in deducing the manifestation of the hyperconjugative effect from inadequate studies of rates of reaction.

THERE are several factors which might affect the substitutional reactivity of a conjugated molecule; these include (i) stabilisation of initial and transition states due to conjugation or hyperconjugation, (ii) steric effects, (iii) the permanent charge distributions, and (iv) the polarisability of electron orbits. Indeed, when as in many hydrocarbons, the charge density is the same at each atom, this last factor appears to be most important. Nevertheless, many properties of unsaturated organic molecules may be correlated qualitatively with the distribution of electrons in the isolated molecules, for the permanent charge distribution reflects the tendency of the different positions to accept or donate electrons for incipient bond formation with nucleophilic or electrophilic reagents. The electron densities are now calculated for propylene and some methylbenzenes by the method of molecular orbitals, the parameters being the same as used previously (Part I).

When overlap is included (Chirgwin and Coulson, *Proc. Roy. Soc., A*, 1950, **201**, 196) the total density of electrons at the μth carbon atom is given by

$$q_\mu = \sum_{j=1}^{m} n_j x_{j\mu} y_{j\mu}$$

where

$$y_{j\mu} = \sum_{\nu} S_{\mu\nu} x_{j\nu}$$

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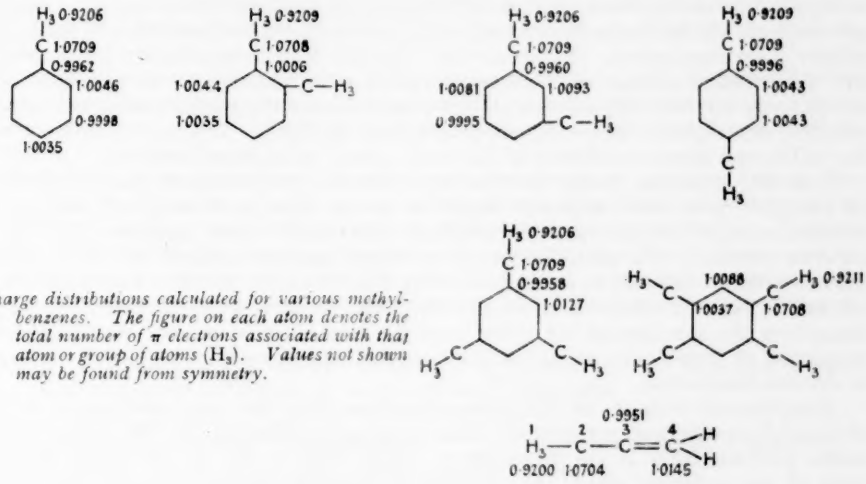
* Part I, preceding paper.

the summation being extended over the occupied orbitals j and the atoms ν, adjacent to μ. The calculated values of the total π-electron densities obtained in this way are shown in the following diagram.

As far as the actual numerical values are concerned, the difference between these compounds and an unsubstituted alternant hydrocarbon is not very large, and considerably smaller than what is obtained when overlap is ignored.



Charge distributions calculated for various methylbenzenes. The figure on each atom denotes the total number of π electrons associated with that atom or group of atoms (H_3). *Values not shown may be found from symmetry.*

Comparison of the electron densities in toluene with those of polymethylbenzenes shows that the additivity which was manifested with respect to hyperconjugation energies applies equally well to the charge distributions. Thus knowing the charge distribution in toluene, that in any polymethylbenzene may at once be written. A similar result was obtained by Coulson and Jacobs (*J.*, 1949, 971) for the charge distributions in aniline and aminostilbenes. They found that the charge migrations in the 4 : 4′-compound were very little different from what would have been expected from a superposition of the migrations in the 4- and 4′-compounds, severally. The same principle was substantiated by Coulson and Longuet-Higgins (*J.*, 1949, 2805) for the charge distributions in some aza-derivatives of naphthalene and anthracene.

Recently, Condon (*J. Amer. Chem. Soc.*, 1948, **70**, 1963) calculated the relative rates of chlorination for a series of polymethylbenzenes and obtained results in good agreement with the experimental values. The additivity found here provides theoretical justification for the assumption made by Condon, *viz.*, that each methyl group in a polymethylbenzene exerts the same activating influence as in toluene. Since the polar effects of methyl groups are small such a result might perhaps have been expected. When, however, two groups of opposing mesomeric character are situated *ortho* or *para* to each other, then mutual interaction is of profound importance.

The attack of electrophilic and nucleophilic reagents on conjugated systems has been discussed from two points of view. On the one hand (Wheland, *J. Amer. Chem. Soc.*, 1942, **64**, 900), the π-electron energies of the transition complexes involved in substitution reactions were computed. It was found that for a given reagent R and a series of different points of attack on a given aromatic A, the reactivity is greater the lower the π-electron energy in the transition state RA. On the other hand, it has been shown (Longuet-Higgins and Coulson, *Trans. Faraday Soc.*, 1947, **43**, 87) that, if two positions in a conjugated molecule differ appreciably in electron density, the centre with the higher charge, q, is more susceptible to attack by electrophilic reagents, whereas nucleophilic reagents substitute more easily at the position of lower electron density. This conclusion, it has

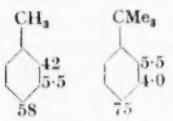
been shown (Coulson and Longuet-Higgins, *Rev. Sci.*, **1947**, **85**, 929), is dependent on the fact that at the moment an anion or cation begins to react on part of a conjugated system the variation of the π-electron energy is directly proportional to the electron density in the region under attack and to the value in this region of the field due to the charge of the reagent. In this way, then, the close correspondence between electron density in the ground state and observed chemical behaviour is explained.

In the case of propylene, " atom 4 " (cf. Figure) has the higher charge density and might be expected to be the centre most easily attacked by an electrophilic reagent. Hence a proton should add across the double bond in such a way that it becomes linked to the greater number of hydrogen atoms. In this way the "normal" Markownikoff addition is accounted for. In a similar manner the electron distribution in toluene may be correlated with its reactivity for, since the *ortho*- and *para*-positions have the greatest calculated electron densities, electrophilic reagents should attack these positions. This is in accordance with the well-known directive influence of the methyl group in the benzene nucleus.

Now the permanent charge distribution in toluene would indicate that in nitration, for example, more *ortho*-compound should be formed than *para*-compound whereas the reverse is actually the case, *i.e.*, the partial rate factor for the *para*- is greater than that for the *ortho*-position. The electronic theory of organic reactions assumes that differences in reaction rates are due only to activation-energy differences, the entropy of activation being constant. Since examination of models shows that in most *ortho*-disubstituted benzene derivatives the substituents are closer than the sum of their van der Waals radii, the proportion of *ortho*-isomer should be less than that calculated from simple considerations of electron distribution.

Experimental evidence for the hyperconjugative effect was early provided by studies of electrophilic substitution reactions. Thus electrophilic substitution of 4-*iso*propyltoluene occurs predominantly at the 2-position, a result which is the reverse of the accepted order of the inductive effect. On the basis of hyperconjugation, however, the position *ortho* to the methyl group should be more susceptible to electrophilic attack than the position *ortho* to the *iso*propyl group, and this was in fact Baker's explanation (*J.*, 1935, 1846). Le Fèvre (*J.*, 1933, 980) on the other hand regarded the results as demonstrating steric repulsion due to increasing size of the alkyl groups. The interpretation therefore is not entirely free from ambiguity.

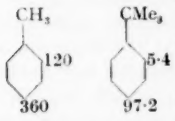
A few years ago it was pointed out (Crawford, *Quart. Reviews*, 1949, **3**, 226) that relative rate data alone provided inadequate evidence for indicating the operation of the hyperconjugative effect. Recently, however, Nelson and Brown (*J. Amer. Chem. Soc.*, **1951**, **73**, 5605) and Cohn, Hughes, Jones, and Peeling (*Nature*, **1952**, **169**, 291) studied the nitration of toluene and *tert.*-butylbenzene. The latter workers determined the isomer distributions as well as the relative rates, thus providing results which may be interpreted unambiguously and with some assurance. The relative rates of nitration are Me : Bu^t = 1·00 : 64 and these figures, when combined with the isomer distributions, gave the partial rate factors shown inset.



Since there are no large differences in the partial rate factors rof the *para* and *meta* positions of these compounds, the large difference for the *ortho* positions is definite proof of the importance of steric requirements for *ortho*-substitution. The slightly greater partial rate factor for the *para*-position of *tert.*-butylbenzene as compared with toluene would seem to show the operation of the inductive effect; this would be expected to be enhanced in *tert.*-butylbenzene as compared with toluene. These results suggest that the hyperconjugative effect is of minor importance in nitration.

Berliner and Berliner (*J. Amer. Chem. Soc.*, 1949, **71**, 1195) found the relative rates of bromination of toluene, ethylbenzene, *iso*propylbenzene, and *tert.*-butylbenzene to be 100 : 70 : 40 : 18, these values being in good agreement with those of de la Mare and Robertson (*J.*, 1943, 279). Berliner and Berliner appreciated that increasing size of the alkyl group might account for their results and therefore considered it. Unfortunately they did not determine isomer distributions under the conditions of their experimentation but used values quoted in the literature. They calculated the partial rate factors for the *para*-

positions only and showed that this position in toluene is almost three and a half times more reactive than the corresponding position in *tert.*-butylbenzene. By combining the above relative rates with the same isomer distribution as used by Berliner the partial rate factors shown inset for the *ortho*-positions were obtained.



The very large decrease on passing from toluene to *tert.*-butylbenzene shows the operation of a marked steric effect. Furthermore comparison of this diminution (120 : 5·4) with that which occurs in nitration (42 : 5·5) shows that the steric effect is probably more pronounced in bromination than in nitration.

The greater reactivity of the *para*-position in toluene as compared with the corresponding position in *tert.*-butylbenzene would perhaps indicate that hyperconjugation is of some significance in bromination. It must be stressed, however, that this conclusion is based on an assumed isomer distribution.

The desirability of determining the *ortho* : *meta* : *para* ratios at the same time as the relative rates is emphasised. In the past, conclusions concerning the manifestation of the hyperconjugative effect have been drawn from rather inadequate rate studies. Further progress in attributing rate changes unambiguously to certain specific electronic or steric influences can only be made when rate differences are studied under conditions which isolate a single simple mechanism and are accompanied by accurate energies and entropies of activation.

Grateful acknowledgment is made to Professor C. A. Coulson, F.R.S., for suggesting the work. His great interest and helpful advice are also much appreciated.

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420. *Hyperconjugation. Part III.* Bathochromic Shifts resulting from Methyl Substitution in Conjugated Systems.*

By V. A. CRAWFORD.

A molecular-orbital calculation of the frequency of absorption of methyl-substituted ethylenes and benzenes has been made and the results compared with experiment. In agreement with Mulliken it is concluded that the red shifts in the spectra result chiefly from hyperconjugation.

IT is well known (Askew, *J.*, 1935, 509; Mohler, *Helv. Chim. Acta*, 1937, **20**, 811; Gillam, *J.*, 1940, 543; Billroth, *Z. physikal. Chem.*, 1936, **33**, *B*, 133; Forster and Wagner, *ibid.*, 1937, **35**, 343) that replacement of the hydrogen atoms of ethylene or aromatic hydrocarbons by alkyl groups results in spectra which are similar in shape to that of the unsubstituted hydrocarbon, but the whole absorption curve is shifted to longer wave-lengths. Shift of the spectrum to longer wave-lengths implies a decrease in the energy-level differences between the ground and excited states. This may result either from a raising of the ground state level, a lowering of the levels of the excited states, or a combination of the two. The reasons for these changes are not as yet completely clear. Thus it has been suggested (Mulliken, *J. Chem. Phys.*, 1939, **7**, 339; *Rev. Mod. Phys.*, 1942, **14**, 265) that the small increase in the resonance stabilisation energy of the alkyl derivatives resulting from hyperconjugation is of the correct order of magnitude to account for the observed spectral shifts. On the other hand (Walsh, *Ann. Reports*, 1947, **44**, 32; *Quart. Reviews*, 1948, **2**, 73) the appearance of the bathochromic shift has been attributed to reduction in ionisation potential of the ethylenic or aromatic centre by "charge transfer" through an inductive mechanism from the alkyl groups. Now charge transfer, or migration of charge, can arise not

* Part II, preceding paper.

only from the inductive effect but also from conjugation and hyperconjugation. Since both types of effect must occur, the present work was undertaken as part of a programme the object of which was to determine the relative importance of the two effects.

Method of Calculation.—In order to explain in detail the more quantitative aspects of spectra, antisymmetrisation is necessary, *i.e.*, the molecular " eigenfunction " of the ground state and the excited state must be multiplied by an appropriate spin function and made completely antisymmetrical with respect to exchange of electrons. The added complication of antisymmetrisation will not be used here, however, for straightforward calculations by the simple LCAO molecular-orbital method have been quite successful in explaining the electronic structure and ultra-violet spectra of molecules. Indeed it has recently been emphasised (Platt, *J. Chem. Phys.*, 1950, **18**, 1168) how accurate can be the simple calculations of the π-electronic spectra of conjugated systems. The numerical values assigned to the parameters were the same as those used in Part I and the computations reported here refer to the hyperconjugative effect only.

Since on excitation the electron spins may be parallel or antiparallel, our simple procedure really predicts the centre of gravity of singlet–triplet pairs for nondegenerate cases, whereas for degenerate cases it predicts the centre of gravity of a whole set of singlets and triplets, *i.e.*, of a configuration. If the approximate singlet–triplet separation ε is known, $\varepsilon/2$ may be added to the prediction to locate the singlet more accurately; or subtracted to locate the triplet. In general, however, this correction cannot be made for it is known in only a few cases.

Substituted ethylenes. Propylene, *cis*-butene, *iso*butene, and 2 : 3-dimethylbut-2-ene (tetramethylethylene) belong respectively to the symmetry groups, C_{1h}, C_{2v}, C_{2v}, D_{2h}.

In the ground state of the molecules the mobile electrons occupy in pairs all the bonding orbitals, the ground state descriptions being as in Table 1, electrons of greatest binding energy being given first.

TABLE 1.

Molecule	Configuration	Ground state
Propylene	$(a'')^2(a'')^2$	A'
cis-Butene	$(b_1)^2(a_2)^2(b_1)^2$	A_1
*iso*Butene	$(b_1)^2(a_2)^2(b_1)^2$	A_1
2 : 3-Dimethylbut-2-ene	$(b_{3u})^2(b_{1g})^2(b_{2g})^2(a_{1u})^2(b_{2u})^2$	A_{1g}

Different excited states are obtained by taking an electron from a bonding orbital and placing it in an anti-bonding one. The first excited state corresponds to the transition from the highest bonding orbital (N) to the lowest anti-bonding one (V_1). The corresponding transition is designated $N \longrightarrow V_1$ and the corresponding excitation energy determines the longest wave-length absorption. Table 2 shows the first excited states, the direction of polarisation being longitudinal.

TABLE 2.

Molecule	Upper state	Absorption process
Propylene	$(a'')(a'')$	$A' \longrightarrow A'$
cis-Butene	$(b_1)(a_2)$	$A_1 \longrightarrow B_2$
*iso*Butene	$(b_1)(b_1)$	$A_1 \longrightarrow A_1$
2 : 3-Dimethylbut-2-ene	$(b_{2u})(b_{1g})$	$A_{1g} \longrightarrow B_{2u}$

The computed energy values corresponding to the $N \longrightarrow V_1$ transition for the methylated ethylenes as well as the observed values are presented in Table 3. Since, as mentioned previously, singlet and triplet levels arise on excitation, the singlet may be more accurately located by adding to the computed excitation energy a quantity $\varepsilon/2$ corresponding to half the singlet–triplet separation.

The experimental values are taken from Mulliken (*Rev. Mod. Physics*, 1942, **14**, 265) who points out that the $N \longrightarrow V$ data refer to $\nu_{max.}$. In combining them with the N-term values given an estimated correction of 0·2 has been added to reduce them to $\nu_{max.}$ values (vertical excitation potentials).

Ionisation potentials. The experimental data show that there is a linear relation between the values for the ground and excited state terms and the number of methyl groups in

a methylated ethylene. However, the initial drop in the N-term value on passing from ethylene to propylene seems to be somewhat greater than that resulting from the further methylation of ethylene. The theoretically computed shifts in term values on the other hand are almost strictly proportional to the number of substituent methyl groups.

TABLE 3. *Term values and spectra of methyl-substituted ethylenes.*

	Experimental			Computed		
	N, ev	V_1, ev	$N \longrightarrow V_1$, ev	N	V_1	$N \longrightarrow V_1$ ev
Ethylene	10·45	3·04	7·61	$\alpha_0 + 0{\cdot}8504\beta_0$	$\alpha_1 - 1{\cdot}4794\beta_0$	$2{\cdot}3298\beta_0$ 7·61
Propylene	9·6	2·66	7·14	$\alpha_1 + 0{\cdot}7964\beta_0$	$\alpha_1 - 1{\cdot}4246\beta_0$	$2{\cdot}2210\beta_0$ 7·25
cis-Butene	9·2	2·38	7·02	$\alpha_2 + 0{\cdot}7470\beta_0$	$\alpha_2 - 1{\cdot}3751\beta_0$	$2{\cdot}1221\beta_0$ 6·93
*iso*Butene	—	—	—	$\alpha'_2 + 0{\cdot}7537\beta_0$	$\alpha'_2 - 1{\cdot}3776\beta_0$	$2{\cdot}1313\beta_0$ 6·96
2 : 3-Dimethylbut-2-ene	8·3	1·72	6·78	$\alpha_4 + 0{\cdot}6684\beta_0$	$\alpha_4 - 1{\cdot}2930\beta_0$	$1{\cdot}9614\beta_0$ 6·40

The computed result recorded in Table 3 show that the hyperconjugative effect raises the ground-state and lowers the excited-state energies. On the other hand, preliminary calculations (*e.g.*, Coulson, " Valence," Oxford Univ. Press, 1952, p. 309) show that the inductive effect raises both the ground-state and the excited-state energies. This co-operation of the two effects on the ground state results in slightly greater shift in N-term values as compared with the V-term values. Because the magnitude of the inductive effect on the excited state is greater than that of the hyperconjugative effect, this results in an overall decrease in experimental V-term values. Since, however, the two effects act in opposition on the excited state, the shifts in V-term values with progressive methylation is smaller than that produced in the ground state.

Theoretical calculation gives the N- and V-term values but only within the additive quantity α which is usually supposed to be constant, at least for a given molecule. If α were the same for different methylated compounds the computations would give directly the changes in N- and V-term values on methyl substitution. Comparison of the computed and experimental ionisation potentials shows that the latter decrease much more rapidly than the former, indicating that $-\alpha$ decreases with methyl substitution. Now it has been shown (Mulliken, *Phys. Review*, 1948, **74**, 76) that, other things being equal, $|\alpha|$ decreases in magnitude with an increase in the number of atoms covered by the molecular orbital. Thus for example there is a progressive decrease in ionisation potential on passing from ethylene through butadiene to benzene. Since hyperconjugation implies that the methyl group may be regarded as part of the conjugated system, a portion of the decrease must result from merely increasing the number of atoms in the conjugated system. Nevertheless, in agreement with that of Mulliken (*Rev. Mod. Physics*, 1942, **14**, 265) the present work indicates that about 0·2 ev of the observed decrease in ionisation potential is attributable to hyperconjugation.

Frequencies. Comparison of the observed and computed excitation energy for ethylene gives a value for β_0 of $-3{\cdot}27$ ev. This value is then used to convert the computed $N \longrightarrow V$ data into ev. It is at once apparent that the computed frequency shifts are of the right order of magnitude and that they are proportional to the number of methyl groups. The experimental shifts are roughly proportional to the number of substituent methyl groups although the initial drop in excitation energy on passing from ethylene to propylene is slightly greater than that resulting from further substitution.

Recently Coulson (*Proc. Phys. Soc.*, 1952, **65**, *A*, 933) examined in a general theoretical manner the shifts in the spectrum resulting from alkyl substitution in hydrocarbons. The influences of the inductive and hyperconjugative effects on the spectral properties are quite distinct, the change in energy from the inductive effect being given by $2ASc_{r1}{}^2\delta\alpha_r$, where A is a positive constant, S the overlap integral, c_{r1} the coefficient c_r for orbital 1 and $\delta\alpha_r$ the change in the coulomb term of the carbon atom to which the methyl group is attached. Since $\delta\alpha_r$ is positive for methyl the above expression shows that the energy shifts resulting from the operation of the inductive effect will always be positive, leading to hypsochromic shifts. On the other hand the hyperconjugative effect on alternant hydrocarbons is always bathochromic. Since here an overall red shift occurs, the red shift due to hyperconjugation must be of larger magnitude than the inductive effect.

From Table 3 it is seen that *iso*butene is predicted to have a slightly greater wave number than *cis*-butene. This is in complete accord with Carr and Stücklen's experimental results (*J. Chem. Phys.*, 1936, **4**, 760) which showed that CHR=CHR has on average a slightly lower wave number for the first band than $CR_2=CH_2$.

Methylbenzenes. The ground state descriptions of these molecules are given in Table 4.

TABLE 4.

	Molecule	Description	Ground state
C_s	Toluene	$(b_1)^2(b_1)^2(a_2)^2(b_1)^2$	A_1
C_{2v}	*o*-Xylene	$(b_1)^2(a_2)^2(b_1)^2(a_2)^2(b_1)^2$	A_1
C_{2v}	*m*-Xylene	$(b_1)^2(a_2)^2(b_1)^2(b_1)^2(a_2)^2$	A_1
D_{2h}	*p*-Xylene	$(b_{3u})^2(b_{1g})^2(b_{3u})^2(b_{2g})^2(b_{1g})^2$	A_{1g}
D_{3h}	Mesitylene	$(a'')^2\underbrace{(e'')^2(e'')^2}(a'')^2\underbrace{(e'')^2(e'')^2}$	A_1
D_{2h}	Durene	$(b_{3u})^2(b_{2g})^2(b_{1g})^2(a_{1u})^2(b_{3u})^2(b_{1g})^2(b_{2g})^2$	A_{1g}

The substituent reduces the symmetry of benzene, resulting in a splitting of the degenerate benzene levels; two close lying states arise, the transition energies for which are recorded in Table 5.

In order to calculate the wave-length and intensity of the near ultra-violet absorption of a substituted benzene, the nature of the transition must be established. In benzene the excitation of an electron from the highest filled orbital to the lowest unoccupied orbital would produce an excited singlet and triplet state each with four-fold degeneracy. When electron repulsion is included the degeneracy is removed and there results a group of three singlet and three triplet states. The energies of excitation as calculated here without

TABLE 5.

Molecule	Upper state	Absorption process	Polarisation	Excitation energy
Toluene	$(b_1)(b_1)$	$A_1 \longrightarrow A_1$	z	$2{\cdot}0671\beta_0$
	$(b_1)(a_2)$	$A_1 \longrightarrow B_2$	y	$2{\cdot}0976\beta_0$
o-Xylene	$(b_1)(a_2)$	$A_1 \longrightarrow B_2$	y	$2{\cdot}0334\beta_0$
	$(b_1)(b_1)$	$A_1 \longrightarrow A_1$	z	$2{\cdot}0636\beta_0$
m-Xylene	$(a_2)(a_2)$	$A_1 \longrightarrow A_1$	z	$2{\cdot}0382\beta_0$
	$(a_2)(b_1)$	$A_1 \longrightarrow B_2$	y	$2{\cdot}0669\beta_0$
p-Xylene	$(b_{1g})(b_{1g})$	$A_{1g} \longrightarrow A_{1g}$	forbidden	$2{\cdot}0075\beta_0$
	$(b_{1g})(b_{3u})$	$A_{1g} \longrightarrow B_{2u}$	y	$2{\cdot}0075\beta_0$
Durene	$(b_{2g})(b_{3u})$	$A_{1g} \longrightarrow B_{1u}$	z	$2{\cdot}0054\beta_0$
	$(b_{2g})(a_{1u})$	$A_{1g} \longrightarrow B_{2u}$	y	$1{\cdot}9507\beta_0$

The yz plane has been taken to correspond to the plane of the molecule. In toluene, *o*-xylene, and *m*-xylene the z-axis is the symmetry axis whereas in *p*-xylene and durene the z-axis has been taken to be the shorter dimension of the molecule.

electron repulsion give the average height of the actual states. A value for β_0 is deduced by identifying the 2600λ band with the computed transition energy of $2{\cdot}1333\beta_0$. This value of β_0 is then combined with the *average* excitation energy to yield the computed frequencies recorded below.

Molecule	Toluene	*o*-Xylene	*m*-Xylene	*p*-Xylene	Benzene
Exptl. λ, Å	2668	2709	2724	2745	2610
Calc. λ, Å	2674	2717	2711	2773	2610
Computed transition energy	$2{\cdot}0823\beta_0$	$2{\cdot}0485\beta_0$	$2{\cdot}0526\beta_0$	$2{\cdot}0075\beta_0$	$2{\cdot}1333\beta_0$

Just as in the case of the methylated ethylenes so here too the computed frequency shifts are of the right order of magnitude. Unfortunately, experiment shows that *o*-xylene suffers the least displacement whereas theory predicts this for *m*-xylene; but the difference is not large. However, in accordance with experiment, theory predicts that of the three xylenes the *para*-isomer experiences the greatest displacement.

It has already been pointed out that the inductive effect alone would result in spectra being displaced to shorter wave-lengths. Since, however, an overall displacement to the visible occurs and since the computed N, V frequency shifts are in fair agreement in both magnitude and direction with experiment, it may be taken that the shifts towards the red are due chiefly to hyperconjugation and not to charge transfer or inductive effects. However, there is evidence (Robertson and Matsen, *J. Amer. Chem. Soc.*, 1950, **72**, 5252) that

in certain molecules the inductive effect might be of the same magnitude as the resonance effect. Results of calculations based solely on the inductive effect will be reported later but in the meantime the following considerations may be noted.

The NH_3^+ group, which certainly promotes a strong inductive effect but is incapable of large-scale participation in a resonance effect, brings about no significant change in the spectrum of benzene. The NO_2 group on the other hand, which like the amine cation is also highly *meta*-directing, is one of the most effective displacing groups. An important point of contrast between these groups is the difference in their ability to participate in actual electron transfer. This would seem to imply that the effects which cause displacement of the bands are similar to, if not identical with, the conjugative as contrasted with the inductive effect.

Furthermore, attention is directed to the fact that in toluene and chlorobenzene two groups as unlike as methyl and chloro behave as auxochromes to the same extent. With chlorine the inductive effect would oppose the contribution of negative charge to the ring. On the other hand, the chlorine atom has electron pairs which may conjugate with the ring π electrons and this latter effect predominates to produce a net auxochromic effect.

This conclusion that where the inductive and conjugative effects occur simultaneously the latter predominates is reinforced by a consideration of the spectroscopy of the chloroethylenes. The inductive effect is usually regarded as being of short range and is therefore likely to be of greater importance in small molecules than large. Yet in the chloroethylenes the electronic levels and ionisation potentials as a whole are shifted to long wavelengths (Walsh, *Trans. Faraday Soc.*, 1945, **41**, 35). The large electronegativity of the chlorine atom would lead one to expect the opposite on a simple inductive-effect basis. The experimentally observed effect must therefore be due to conjugation between the electrons of the double bond and the lone pair of the chlorine atom. Furthermore, as the number of chlorine atoms is increased the increasing conjugation of the π electrons of the double bond with the $p\pi$ electrons of chlorine displaces the transition more and more to long wave-lengths. So, for example, in the dichloro-compound the C=C bond is subjected to twice as great an inductive effect as in vinyl chloride, yet despite this the first maximum occurs at longer wave-lengths.

This conclusion that the bathochromic frequency shifts are due to a delocalisation rather than to an inductive effect has recently been established on a semi-quantitative basis by Daub and Vandenbelt (*J. Amer. Chem. Soc.*, 1947, **69**, 2714; 1949, **71**, 2414), who correlated the displacement of the primary band with the direction and extent of resonance interaction between the substituent groups of *para*-disubstituted benzene derivatives. The available evidence therefore seems to support Bateman and Koch's contention (*J.*, **1944**, 600) that double-bond absorption is very much less sensitive to inductive influences than has hitherto been supposed.

The results reported here have been obtained by use of the simple LCAO treatment, including overlap, but excluding antisymmetrisation and allowance for configurational interaction. This interaction changes the energies and wave-function of two neighbouring states which have the same symmetry. Such states mix so that the lower state has its energy lowered further and the upper state has its energy raised, the effects being more marked the closer the two states are together. This effect is particularly important in the case of excited states for frequently the energy differences between excited states are to a large extent due to electron interaction. Coulson, Craig, and Jacobs (*Proc. Roy. Soc., A*, 1950, **202**, 498; 1951, **206**, 287) have demonstrated its importance although for a comparative study its omission is probably not too serious.

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421. *The Preparation of Some* m- *and* p-*Alkylanilines.*

By R. Long and K. Schofield.

m- and *p*-Alkylanilines have been prepared in high yields by catalytic reduction of *m*- and *p*-acetamidophenyl alkyl ketones in acetic acid, with palladium–barium sulphate as catalyst and perchloric acid as activator.

We required a number of *m*- and *p*-alkylanilines for synthetical work. Recorded preparations of the *p*-compounds from alkylbenzenes, from aniline, or *N*-alkylarylamines, or of *m*-alkylanilines from their *p*-analogues, are tedious. Alkyl *m*- and *p*-aminophenyl ketones would be convenient starting materials. Reduction of such compounds has been effected by the Huang-Minlon modification of the Wolff–Kishner reduction (Buu-Hoï, Eckert, and Royer, *Compt. rend.*, 1951, **232**, 1356; 1951, **233**, 1461; Linnell and Vora, *J. Pharm. Pharmacol.*, 1951, **3**, 670; Nineham, *J.*, 1952, 635) though yields were not reported. The Clemmensen reduction is unsatisfactory (von Braun and Weissbach, *Ber.*, 1929, **62**, 2416; Day, *J.*, 1930, 252; Brady and Day, *J.*, 1934, 114; Taylor and Watts, *J.*, 1952, 1123).

We achieved a practicable synthesis of the desired compounds by hydrogenating the acetamidophenyl ketones at 95° in presence of palladium–barium sulphate in acetic acid containing perchloric acid (Rosenmund and Karg, *Ber.*, 1942, **75**, 1850). The *p*-acetamidoketones are readily available from Friedel–Crafts reactions, and we obtained the *m*-compounds by catalytic reduction of the nitro-ketones (Leonard and Boyd, *J. Org. Chem.*, 1946, **11**, 405; Marvel and Overberger, *J. Amer. Chem. Soc.*, 1946, **68**, 185; Marvel, Allen, and Overberger, *ibid.*, p. 1089).

Direct hydrogenation of the nitro- or amino-ketones under the conditions used with the acetamido-compounds gave small amounts of alkylanilines and large quantities of high-boiling oils. The latter, apparently secondary amines, were formed exclusively in the absence of perchloric acid, and probably arose from the initially formed primary amine by condensation with unreduced ketone and further reduction. Such processes are hindered by protonisation by perchloric acid, and of course prevented by acetylation.

Papa, Schwenk, and Whitman (*J. Org. Chem.*, 1942, **7**, 587) reduced *m*-nitroacetophenone to *m*-ethylaniline with Raney alloy and sodium hydroxide. We found it better to use amino-ketones and obtained moderate yields of *p*-alkylanilines by this method, which was, however, less satisfactory in the *m*-series. The reaction is very inconvenient except on the small scale. Clemmensen reduction of *m*-nitroacetophenone gave only a poor yield (9·5%) of *m*-ethylaniline.

Experimental

Ethereal extracts were dried with anhydrous Na_2SO_4. 72% Perchloric acid was used.

Reductions of m-*Nitroacetophenone.*—(i) *With Raney alloy.* The most successful of a number of experiments was carried out as follows. The ketone (50 g.) in ethanol (125 c.c.) and aqueous sodium hydroxide solution (1750 c.c.; 10%) was heated and stirred under reflux at 90—100° during the addition of Raney alloy (150 g.) as quickly as gas evolution permitted (various surface active agents were examined, but failed to mitigate frothing). After the addition the mixture was heated and stirred for several hours and then steam-distilled. The distillate was saturated with salt, and the product was isolated by ether and distilled, giving 39% of *m*-ethylaniline, b. p. 93—95°/6 mm. The *picrate* formed yellow needles, m. p. 170—171° (Found: C, 48·6; H, 4·3. $C_8H_{11}N,C_6H_3O_7N_3$ requires C, 48·0; H, 4·0%), from aqueous methanol. The *toluene*-p-*sulphonyl* derivative crystallised from the same solvent, as colourless needles, m. p. 80° (Found: C, 65·7; H, 6·3. $C_{15}H_{17}O_2NS$ requires C, 65·4; H, 6·2%). The yield of *m*-ethylaniline decreased in larger-scale experiments, 11·4% being obtained from 150 g. of the ketone. Reduction with Raney alloy in acid solution gave mainly *m*-aminoacetophenone, with a little of the alkyl compound.

(ii) *With palladium–charcoal.* When the nitro-ketone (2 g.), methanol (40 c.c.), and the catalyst (0·3 g.) were shaken with hydrogen, 3 mols. were rapidly absorbed, and uptake then ceased. Filtration and concentration of the solution gave *m*-aminoacetophenone (1·5 g.).

(iii) *With palladium–barium sulphate.* (*a*) The ketone (20 g.), methanol (300 c.c.), and catalyst (2 g.), treated as in (ii), gave 96% of *m*-aminoacetophenone.

(*b*) The ketone (5 g.), acetic acid (50 c.c.), perchloric acid (2·5 c.c.), and catalyst (5 g.) were shaken with hydrogen at 95°. 5 Mols. of hydrogen were absorbed in 1·5 hr., and after that a very slow continuous uptake was observed. Filtration, basification, and ether-extraction provided a dark oil (2·5 g.) which gave red oily drops with nitrous acid, but remained immiscible when refluxed with concentrated hydrochloric acid. From the latter treatment, by basification and ether-extraction, an oil resulted which on distillation yielded *m*-ethylaniline (0·2 g.), b. p. 97—98°/8 mm., and then a viscous liquid, b. p. *ca.* 190°/8 mm. In a similar experiment on 2 g. of the ketone at room temperature, in which reduction was interrupted when 5 mols. of hydrogen had been absorbed, 0·5 g. of the primary amine was obtained. When the perchloric acid was omitted the high-boiling oil was the sole product. Similar results attended hydrogenation in acetic acid under pressure. The ketone (5 g.), acetic acid (100 c.c.), and catalyst (5 g.) were treated with hydrogen at 130 atm. Reduction to *m*-aminoacetophenone occurred in 20 min. The temperature was then raised to 200°, and kept there until absorption ceased (4 hr.). Worked up as before the product gave a small primary amine fraction, and a large amount of viscous oil, b. p. 192—198°/10 mm., soluble in hydrochloric acid and giving the nitrosamine test.

m-Nitropropiophenone similarly gave small amounts of *m*-propylaniline, b. p. 118—119°/12—13 mm. (Found: C, 80·5; H, 10·1. Calc. for $C_9H_{13}N$: C, 80·0; H, 9·7%) [the *picrate* formed glistening yellow flakes, m. p. 155° (Found: C, 48·95; H, 4·5. $C_9H_{13}N,C_6H_3O_7N_3$ requires C, 49·45; H, 4·4%), from aqueous methanol], and variable amounts of a secondary amine, b. p. *ca.* 200°/9—10 mm. *m*-Nitrobutyrophenone in the absence of perchloric acid gave a viscous oil, b. p. 216—218°/11 mm. (Found: C, 75·9; H, 9·95; N, 6·8%), and only traces of a primary amine.

Reduction of m-*Acetamidoacetophenone.*—The amide (3 g.), palladium–barium sulphate (3 g.) (further experiments showed it satisfactory to use 1 g. of catalyst to 5 g. of the amide), acetic acid (30 c.c.), and perchloric acid (3 c.c.) were shaken at 95° with hydrogen. After 1 hr. uptake ceased. The material isolated by basification and ether-extraction was refluxed with hydrochloric acid (80 c.c.; 8N) for ½ hr., and a light brown oil (2·2 g.) was recovered by basification and ether-extraction. Distillation gave *m*-ethylaniline (1·6 g., 78%), b. p. 100—102°/9—10 mm., as the sole product.

m-*Acetamidopropiophenone.*—*m*-Nitropropiophenone (20 g.), methanol (400 c.c.), and palladium–charcoal (1·5 g.) were shaken with hydrogen, uptake (3 mols.) of which ceased after 4 hr. Filtration, evaporation, and distillation gave *m*-aminopropiophenone (13·3 g.) as a pale yellow oil, b. p. 167—169°/9—10 mm. (Elson, Gibson, and Johnson, *J.*, 1930, 1128, gave b. p. 168—169°/15 mm.), which slowly crystallised. A boiling solution of the amine (10 g.) in benzene (35 c.c.) was treated slowly with acetic anhydride (10 c.c.). *m*-Acetamidopropiophenone (10·7 g., 84%), m. p. 92° (Keneford and Simpson, *J.*, 1948, 354, give m. p. 92—93°), crystallised from the filtered solution.

Reduction of m-*Acetamidopropiophenone.*—The acetyl derivative (5 g.), acetic acid (50 c.c.), palladium–barium sulphate (1 g.), and perchloric acid (5 c.c.) were treated with hydrogen at 95°. Uptake (1250 c.c.) of the latter was complete in 90 min., and the product was worked up as described for *m*-acetamidoacetophenone, giving *m*-aminopropylbenzene (3·1 g., 87%) as an oil, b. p. 107—110°/8 mm. It was identified as its picrate.

Reduction of m-*Amino-* and m-*Nitro-butyrophenone.*—(i) The nitro-compound (40 g.) in methanol (400 c.c.), with palladium–charcoal (3 g.), was rapidly reduced with evolution of heat to *m*-aminobutyrophenone (29·2 g., 86%), b. p. 178°/9—10 mm. (Elson *et al.* give b. p. 179—180°/16 mm.).

(ii) *With Raney alloy.* *m*-Aminobutyrophenone (10·3 g.), methanol (400 c.c.), and aqueous sodium hydroxide solution (900 c.c.; 10%), at 95°, were stirred and treated with Raney alloy (90 g.; added as pellets to enable reaction to proceed in the bulk of the liquid), giving in the usual way *m*-butylaniline (4·55 g.), b. p. 125—128°/9—10 mm., and some unchanged starting material. The benzoyl derivative formed plates, m. p. 68—70° (Reilly and Hickinbottom, *J.*, 1920, **117**, 107, give m. p. 68°). On the large scale the yield became insignificant, *m*-aminobutyrophenone being the chief product, as it was when *m*-nitrobutyrophenone was similarly reduced.

Reduction of m-*Acetamidobutyrophenone.*—The amide was prepared by using acetic anhydride in boiling benzene, as for *m*-acetamidopropiophenone, or with acetic anhydride alone at 95°. Initially obtained as a yellow oil (95% by the first method), b. p. 244—246°/9 mm., m-*acetamido-*

butyrophenone slowly crystallised, and formed needles, m. p. 82—83° (Found: C, 69·9; H, 7·3. $C_{12}H_{15}O_2N$ requires C, 70·2; H, 7·4%), from ether–light petroleum. By the second method, with seeding, the compound was obtained in 69% yield after removal of excess of acetic anhydride.

The amide (3 g.), palladium–barium sulphate (1 g.), acetic acid (30 c.c.), and perchloric acid (3 c.c.) were shaken with hydrogen at 95°, and the product was worked up as usual. *m*-Butylaniline (1·8 g., 72%), b. p. 124—125°/9 mm., was identified as its benzoyl derivative.

Reductions of p-*Aminoacetophenone.*—(i) *With Raney alloy.* The ketone (10 g.), ethanol (500 c.c.), and aqueous sodium hydroxide (500 c.c.; 10%), treated with Raney alloy (50 g.) and processed in the usual way, gave *p*-ethylaniline (4·6 g., 51%), b. p. 100—103°/11 mm.

(ii) *Catalytic.* The ketone (5 g.), acetic acid (50 c.c.), and palladium–barium sulphate (2 g.) were treated as usual at 95°. The rate of uptake of hydrogen gradually decreased, but on addition of more catalyst (2 g.) and perchloric acid (2 c.c.) absorption was resumed and continued until approx. 5 mols. had been taken up. Basification and ether-extraction afforded a brown oil (4·5 g.). Attempted distillation suggested the presence of an acetyl derivative, so the oil (4·1 g.) was boiled with concentrated hydrochloric acid (10 c.c.), and the product was isolated by basification and ether-extraction. Distillation gave *p*-ethylaniline (1·35 g.), b. p. 100°/10—11 mm. (reduction of *p*-nitroethylbenzene gave material b. p. 100—102°/10 mm.), and a viscous oil, b. p. *ca.* 200°/10—11 mm.

Reductions of p-*Aminopropiophenone.*—(i) *With Raney alloy.* The amine (55 g.), ethanol (950 c.c.), and aqueous sodium hydroxide (1650 c.c.; 10%) when reduced in the usual way with Raney alloy (165 g.) gave *p*-propylaniline (31 g., 62%), b. p. 108—110°/9—10 mm.

(ii) *Catalytic.* When the ketone (5 g.), palladium–barium sulphate (2 g.), acetic acid (50 c.c.), and perchloric acid (2 c.c.) were hydrogenated at 95° as usual, reaction ceased when 1250 c.c. of hydrogen had been consumed, but on addition of more catalyst (2 g.) reduction continued, a total of 1570 c.c. of hydrogen being absorbed. Filtration, basification, and ether-extraction gave an oil (4·0 g.) which when crystallised from benzene–ligroin (b. p. 60—80°) gave plates of *p*-acetamidopropylbenzene, m. p. 93—94° (Found: C, 74·9; H, 8·7. Calc. for $C_{11}H_{15}ON$: C, 74·5; H, 8·5%) (Willgerodt and Sckerl, *loc. cit.*, give m. p. 87°). In a second identical experiment the crude product (4·0 g.) was boiled with concentrated hydrochloric acid (20 c.c.). The product, isolated by basification and ether-extraction, gave *p*-propylaniline (2·3 g., 50%), b. p. 111—113°/10—11 mm., and a viscous oil, b. p. 220—230°/10—11 mm.

Reduction of p-*Acetamidopropiophenone.*—*p*-Aminopropiophenone (12 g.) in boiling benzene (200 c.c.) was treated gradually with acetic anhydride (12 c.c.). Crystals were deposited immediately, and after being kept overnight *p*-acetamidopropiophenone (15·7 g., 96%), m. p. 168°, was collected. When this (5 g.), acetic acid (50 c.c.), palladium–barium sulphate (1 g.), and perchloric acid (5 c.c.) were hydrogenated at 95°, 1225 c.c. of hydrogen were absorbed in 1 hr., and reduction then ceased. In the usual way *p*-propylaniline (3·05 g., 78%), b. p. 107—108°/8 mm., was isolated, and identified as its acetyl derivative, m. p. 93—95°, alone and mixed with that described above.

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422. *Formation of Sulphites, Phosphites, and Phosphates of Alcohols containing an Aryl Group.*

By W. Gerrard and B. D. Shepherd.

2-Phenylethanol, 3-phenylpropanol, 1 : 3-diphenylpropan-2-ol, 1-phenylpropan-2-ol, 1 : 2-diphenylethanol, and benzyl alcohol behave as does butan-1-ol in that only sulphite and base hydrochloride are quickly formed at −10° by thionyl chloride and pyridine, whereas 1-phenylethanol, 1-2′-naphthylethanol, and diphenylmethanol give the chloride RCl concurrently, although at −78° only diphenylmethanol still does so. Phosphorus oxychloride and pyridine give base hydrochloride and phosphate with the first four alcohols named, as does butan-1-ol; but the others give chloride RCl and little if any phosphate. Phosphorus trichloride and pyridine give base hydrochloride and phosphite with all the alcohols, as does butan-1-ol.

For the purpose of describing alcohol–inorganic non-metallic halide systems it is desirable to compare the behaviour of the alcohol with that of butan-1-ol or of 1-phenylethanol in the same system (Gerrard, *J.*, 1944, 85; 1945, 106; 1946, 741; Gerrard and Woodhead, *J.*, 1951, 519; Gerrard and Lappert, *ibid.*, p. 1020; Gerrard and Phillips, *Chem. and Ind.*, 1952, 540). During the addition of thionyl chloride (0·5 mol.) to an ethereal solution of alcohol (1 mol.) and pyridine (1 mol.) there was rapid reaction, even at −78°, probably by the steps: $ROH,NC_5H_5 + SOCl_2 \longrightarrow RO{\cdot}SOCl + C_5H_5N,HCl$; $ROH,NC_5H_5 + RO{\cdot}SOCl \longrightarrow SO(OR)_2 + C_5H_5N,HCl$. At −10°, but not at −78°, 1-phenylethanol and 1-2′-naphthylethanol gave also chloride, RCl, whereas diphenylmethanol still gave some chloride at −78°. If 1-chloro-1-phenylethane came from the intermediate chlorosulphinate the reaction must have been fast at −10°, for it was competing with the rapid second reaction. Furthermore, when the alcohol is added to thionyl chloride alone, the formation of chloride RCl is so fast at −10° that tangible evidence of the formation of the chlorosulphinate has still to be secured. Although 1 : 2-diphenylethanol and benzyl alcohol both have a phenyl group attached to the alcoholic carbon atom, they gave only the sulphite at −10°.

When phosphorus oxychloride (1 mol.) was added to the alcohol (3 mol.) and pyridine (3 mol.) in ether there were two types of reaction. Alcohols having an aryl group attached to the alcoholic carbon atom (nos. 5—9, see Table 4) gave alkyl chloride, unchanged alcohol, and little or no alkyl phosphate, all the phosphorus tending to be with the base in the precipitate, whereas the other alcohols behaved as does butan-1-ol and cleanly gave trialkyl phosphate and base hydrochloride. It is known (unpublished work) that reaction of this oxychloride in the presence of pyridine is slower than that with thionyl chloride and phosphorus trichloride, and the rate falls off perceptibly for the second and especially the third step. It appears that the formation of alkyl chloride is faster when the reactivity of the alcoholic carbon atom is increased by attachment of an aryl group.

In the phosphorus trichloride systems all the alcohols resembled butan-1-ol in that all chlorine was quickly precipitated as base hydrochloride, and the phosphorus was retained as trialkyl phosphite. The phosphites were readily dealkylated (1 group) by hydrogen chloride, and with compounds containing an aryl group attached to the alcoholic carbon atom (5—9) the process readily went further:

$$P(OR)_3 + HCl \longrightarrow P(OH)(OR)_2 + RCl \longrightarrow P(OH)_2(OR) + RCl \longrightarrow P(OH)_3 + RCl$$

1 : 3-Diphenylpropan-2-ol requires special mention. Not only was there some hindrance to the formation of the phosphite (probably concerning the last step), but the interaction between the phosphite and hydrogen chloride was comparatively slow. There was some evidence for the existence of the compound $P(OR)_3,3HCl$, as though each oxygen atom was being hydrogen-bonded (cf. Gerrard and Whitbread, *J.*, 1952, 914).

Experimental

Light petroleum had b. p. 40—60°, and ligroin, b. p. 90—120°.

Interaction with Thionyl Chloride in the Presence of Pyridine.—A standardised procedure was followed with respect to time of addition, total reaction time, concentration, and temperature.

To a solution of the alcohol (0·05 mole) and pyridine (0·05 mole) in ether (30 ml.) at −10° (or −78°) thionyl chloride (0·025 mole) was added dropwise (20—30 min.), with shaking. After a total time of 1 hr., the mixture was filtered. The precipitate, after thorough and rapid washing with dry ether, was kept in a vacuum-desiccator until its weight became constant, and analysed without further purification. The filtrate was concentrated to constant weight under reduced pressure at room temperature. Distillation of the residue was attempted. Purification of the sulphite in nearly every case was difficult, owing to limited thermal stability; but the essential points to establish were the fates of chlorine and sulphur and the degree of completion of the reaction. Data are recorded in Table 1, and in the following notes.

TABLE 1.

No.	Alcohol	Temp.	Pyridine hydrochloride Wt., g.	Found, % °Cl	Found, % C_5H_5N	Residue, g. Found	Residue, g. Calc.	Sulphite dist'd, yield, %
1	2-Phenylethanol	−10°	5·50	30·6	67·8	7·10	7·25	89·0
		−78	5·60	30·0	67·5	7·00	7·25	85·7
2	3-Phenylpropanol	−10	5·65	29·8	67·5	7·92	7·95	90·0
		−78	5·50	29·2	66·0	7·35	7·95	85·0
3	1 : 3-Diphenylpropan-2-ol	−10	5·36	30·5	67·1	11·18	11·75	—
		−78	5·33	29·3	66·0	10·95	11·75	—
4	1-Phenylpropan-2-ol	−10	5·61	30·1	66·6	7·70	7·95	86·2
		−78	6·09	27·5	59·0	7·35	7·95	86·6
	(in pentane)	−10	5·64	30·4	67·5	7·85	7·95	92·2
5	1 : 2-Diphenylethanol	−10	5·39	29·9	67·5	10·47	11·05	—
		−78	5·57	30·2	67·0	10·10	11·05	—
6	Benzyl alcohol	−10	5·50	30·3	68·4	6·36	6·55	81·0
		−78	5·55	30·3	67·3	6·32	6·55	87·0
7	1-Phenylethanol	−78	5·60	29·1	64·5	6·77	7·25	—
8	1-2′-Naphthylethanol	−10	3·70	29·2	67·4	—	—	—
		−78	5·90	29·0	67·2	9·00	9·75	—
9	Diphenylmethanol	−10	3·46	28·0	39·0	—	—	—
		−78	5·15	29·4	64·5	—	—	—
		Calc.:	5·77	30·7	68·4	—	—	—

(1) Di-(2-phenylethyl) sulphite had b. p. 162—165°/0·5 mm., n_D^{15} 1·5510 (Found: C, 66·7; H, 6·5; S, 10·5. Calc. for $C_{16}H_{18}O_3S$: C, 66·3; H, 6·2; S, 11·0%).

(2) Di-(3-phenylpropyl) sulphite had b. p. 185—190°/0·3 mm., n_D^{18} 1·5423 (Found: SO_2, 19·4. Calc. for $C_{18}H_{22}O_3S$: SO_2, 20·1%).

(3) The reactions both at −10° and at −78° were not quite complete; a filtrate residue (Found: SO_2, 12·2. Calc. for $C_{30}H_{30}O_3S$: SO_2, 13·6%) was obtained.

(4) *Di-(1-methyl-2-phenylethyl) sulphite* had b. p. 158—160°/0·1 mm., $n_D^{21\cdot5}$ 1·5351, d_4^{20} 1·1104, α_D^{16} +5·00° ($l = 1$; from ROH, α_D^{16} −10·60°) (Found: C, 68·5; H, 7·0; S, 9·8. $C_{18}H_{22}O_3S$ requires C, 67·9; H, 6·9; S, 10·1%). Hydrolysis by steam-distillation from aqueous potassium hydroxide (20% w/v) afforded the alcohol, b. p. 96°/10 mm., α_D^{16} −9·92° ($l = 1$), thus showing no significant loss in rotatory power in either preparation or hydrolysis of the sulphite.

(5) No alkyl chloride was formed. *Di-(1 : 2-diphenylethyl) sulphite* had m. p. 96—99° (from ligroin) (Found: C, 76·1; H, 5·9; S, 6·45; SO_2, 13·6. $C_{28}H_{26}O_3S$ requires C, 76·1; H, 5·9; S, 7·25; SO_2, 14·4%).

(6) Dibenzyl sulphite had b. p. 152°/0·4 mm., n_D^{25} 1·5590 (Found: S, 11·9. Calc. for $C_{14}H_{14}O_3S$: S, 12·2%).

(7) The special point with this alcohol is that, whereas 1-chloro-1-phenylethane was formed together with the sulphite at −10° (Gerrard, *J.*, 1944, 90), it is now shown that at −78° base hydrochloride accounted for nearly all halogen, and no alkyl chloride was detected in the filtrate residue, which was kept at 60°/1 mm. for 1 hr. (Found: SO_2, 20·9. Calc. for $C_{16}H_{18}O_3S$: SO_2, 22·1%). Dry hydrogen chloride was passed into the sulphite (5·72 g.) at −10° for 2·5 hr. From the dried ethereal extract of the mixture after treatment with water, 1-chloro-1-phenylethane (4·53 g., 82%), b. p. 69—71°/10 mm., n_D^{17} 1·5277 (Found: Cl, 25·0. Calc. for C_8H_9Cl: Cl, 25·25%), was obtained. The same chloride (4·97 g., 85%) (Found: Cl, 25·15%) was obtained when the sulphite (6·02 g., 1 mol.) was kept with thionyl chloride (1 mol.) for 2 hr. at −10°, sulphur dioxide being evolved, and volatile matter being finally removed at

$-10°/0{\cdot}1$ mm. (trap). Furthermore, the same chloride (6·47 g., 92%), b. p. 66—71°/10 mm. (large middle cut, b. p. 67°/9 mm.) (Found: Cl, 25·25%), was obtained when dry hydrogen chloride was passed into the alcohol (6·10 g.) (2 hr. at $-10°$), water treatment being given before distillation. No unchanged alcohol was detected.

(8) At $-10°$ 1-chloro-1-2′-naphthylethane (2·90 g., 30%), b. p. 95°/0·1 mm., m. p. 62—63° (from light petroleum) (Found: Cl, 17·7. Calc. for $C_{12}H_{11}Cl$: Cl, 18·6%), and the impure alcohol (2·08 g., 24%), b. p. 83°/0·1 mm., m. p. 37—39° (Found: Cl, 3·2%), were obtained. At $-78°$, however, no alkyl chloride could be detected, and the viscous, golden residue was heated to 40°/0·1 mm. (Found: SO_2, 16·3. Calc. for $C_{24}H_{22}O_3S$: SO_2, 16·4%).

(9) Alkyl chloride was found both at $-10°$ and at $-78°$. At $-10°$ the precipitate (5·23 g.) was contaminated with a water-insoluble solid which, when dried, afforded diphenylmethanol (1·77 g., 19·2%), m. p. 66—67°, mixed m. p. 65—67°. From the filtrate were obtained chlorodiphenylmethane (3·55 g., 35·1%), b. p. 88—92°/0·1 mm. (Found: Cl, 16·1. Calc. for $C_{13}H_{11}Cl$: Cl, 17·5%), and bisdiphenylmethyl ether (2·12 g., 24%), b. p. 185°/0·1 mm., m. p. 108—109° (from ligroin) (Found: C, 89·2; H, 6·5. Calc. for $C_{26}H_{22}O$: C, 89·1; H, 6·3%). At $-78°$ the precipitate (6·20 g.) contained this ether (1·05 g.), m. p. 107—109°, mixed m. p. 106—107°. The filtrate residue (Found: SO_2, 7·4%) afforded chlorodiphenylmethane (1·11 g., 11%), b. p. 96°/0·2 mm. (Found: Cl, 16·5%), and a tar (7·0 g.).

Phosphorus Trichloride–Pyridine System.—To the alcohol (0·10 mole) and pyridine (0·10 mole) in ether phosphorus trichloride (0·034 mole) in ether (10—20 ml.) was added with shaking during 15 min. After a total time of 1 hr., the precipitate was separated. The filtrate was concentrated to constant weight at 15—20°/15 mm., and distillation attempted. The tendency for the phosphite to precipitate with the pyridine hydrochloride at $-78°$ made separation under anhydrous conditions difficult. The results are summarised in Table 2, and in the following notes.

TABLE 2.

No.	Alcohol	Temp.	Pyridine hydrochloride Wt., g.	Found, % Cl	Found, % C_5H_5N	Phosphite residue, g. Found	Calc.	Dist'd yield, %
1	2-Phenylethanol	−10°	11·57	29·8	67·2	13·00	13·13	80·80
		−78	11·96	28·4	61·4	12·90	13·13	86·30
2	3-Phenylpropanol	−10	11·27	30·8	68·2	14·65	14·50	85·4
		−78	12·42	27·4	59·7	13·90	14·50	76·0
3	1 : 3-Diphenylpropan-2-ol	−10	11·15	30·6	68·2	22·5	22·13	—
4	1-Phenylpropan-2-ol	−10	11·30	29·2	64·5	14·80	14·50	88·3
		−10	11·20	30·7	67·9	14·92	14·50	85·5
		−78	11·60	29·0	64·0	14·92	14·50	83·0
5	1 : 2-Diphenylethanol	−10	11·35	29·6	64·2	21·60	20·70	D
		−10	11·15	30·2	66·5	20·70	20·70	—
6	Benzyl alcohol	−10	11·24	30·7	68·0	12·10	11·76	—
		−10	11·33	30·0	67·8	11·70	11·76	89·3
		−78	11·90	28·9	63·0	11·60	11·76	76·60
7	1-Phenylethanol	−10	11·45	29·0	64·2	13·05	13·13	—
		−78	11·85	28·4	64·8	12·60	13·13	—
8	1-2′-Naphthylethanol ...	−10	11·40	30·2	68·6	18·10	18·14	—
9	Diphenylmethanol	−10	11·40	30·0	67·0	19·80	19·30	—
		Calc.:	11·55	30·7	68·4	—	—	—

(1) *Tri-2-phenylethyl phosphite* had b. p. 162—171°/0·05 mm., n_D^{25} 1·5550 (Found: P, 8·1. $C_{24}H_{27}O_3P$ requires P, 7·9%). Hydrogen chloride and the phosphite (4·83 g.) at $-10°$ afforded 1-chloro-2-phenylethane (76%), b. p. 75°/10 mm. (Found: Cl, 25·5. Calc. for C_8H_9Cl: Cl, 25·25%), and *di-2-phenylethyl hydrogen phosphite* (95·6%), b. p. 147°/0·05 mm., n_D^{26} 1·5429 (Found: P, 10·7. $C_{16}H_{19}O_3P$ requires P, 10·7%).

(2) *Tri-3-phenylpropyl phosphite*, b. p. 195—200°/0·05 mm., n_D^{18} 1·5480 (Found: P, 7·05. $C_{27}H_{33}O_3P$ requires P, 7·1%), with hydrogen chloride gave 1-chloro-3-phenylpropane (72%), b. p. 90°/10 mm. (Found: Cl, 23·1. Calc. for $C_9H_{11}Cl$: Cl, 23·0%), *di-3-phenylpropyl hydrogen phosphite* (85%), b. p. 186°/0·2 mm., n_D^{14} 1·5382 (Found: P, 9·5. $C_{18}H_{23}O_3P$ requires P, 9·8%), and the phosphite (13·2%), b. p. 210°/0·1 mm., n_D^{21} 1·5428. Dealkylation (one group) was more nearly complete at 15°, the yield of hydrogen phosphite then being 91%.

(3) Presumably because the removal of the third chlorine atom was perceptibly slower in this case, precipitation of base hydrochloride was incomplete (85%) after the stated time. After 3 hr. at 15° the precipitate (91·5%) increased to 98% when the volume of solution was reduced to half. After being at 15°/0·1 mm. for 2 hr., the filtrate residue weighed 22·10 g. (Calc.: 22·13 g.) (Found: P, 4·63%). In a further experiment, base hydrochloride (11·15 g., 97%) (Found: Cl, 30·6; C_5H_5N, 68·2%) and *tri*-(1-*benzyl*-2-*phenylethyl*) *phosphite* (22·50 g.) (Found: P, 4·71. $C_{45}H_{45}O_3P$ requires P, 4·67%) were obtained after the mixture had been at −10° for 1 hr. and 15° for 16 hr. Decomposition of the phosphite occurred at 120—180°/0·2 mm.; 1 : 3-diphenylpropene, b. p. 88°/0·01 mm., n_D^{19} 1·5933, which gave 1 : 2-dibromo-1 : 3-diphenylpropane, m. p. 109—110° (Found: C, 50·6; H, 4·0; Br, 45·1. Calc. for $C_{15}H_{14}Br_2$: C, 50·9; H, 4·0; Br, 45·1%), was obtained.

Unusual phenomena attended the passage of hydrogen chloride into this phosphite, the unstable compound $P(OR)_3,3HCl$ being precipitated. When hydrogen chloride was passed (2 hr.) into the phosphite (6·25 g.) in ether (10 c.c.) at −10°, the white precipitate weighed 3·80 g. (immediate analysis: Cl, 12·6%), the readily ionisable chlorine decreasing in amount by the time a second specimen could be weighed (Found: Cl, 11·7; P, 4·45. Calc. for $C_{45}H_{45}O_3P,3HCl$: Cl, 13·75; P, 4·0%). After 5 hr. the material became sticky (Found: Cl, 10·4%), and after several days crystallisation from light petroleum gave *di*-(1-*benzyl*-2-*phenylethyl*) *hydrogen phosphite* as needles, m. p. 77—79° (Found: P, 6·7. $C_{30}H_{31}O_3P$ requires P, 6·6%). The first filtrate residue after being at 70°/0·1 mm. weighed 2·70 g. (Found: Cl, 1·4; P, 4·41%).

(4) *Tri*-(1-*benzylethyl*) *phosphite* had b. p. 181°/0·05 mm., n_D^{19} 1·5364 (Found: P, 7·8. $C_{27}H_{33}O_3P$ requires P, 7·1%). The phosphite, α_D^{21} +21·12° (l = 1) (from ROH, α_D^{16} +26·72°), afforded, on hydrolysis with aqueous potassium hydroxide, the alcohol, α_D^{16} +26·32°, and with hydrogen chloride gave 2-chloro-1-phenylpropane (64·5%), b. p. 80°/15 mm., n_D^{16} 1·5213, α_D^{16} −22·60° (l = 1), and *di*-(1-*benzylethyl*) *hydrogen phosphite* (92·4%), b. p. 147°/0·02 mm. n_D^{20} 1·5291, α_D^{20} +21·68° (Found: P, 9·8. $C_{18}H_{23}O_3P$ requires P, 9·8%). Passage of hydrogen chloride into this ester did not give rise to any isolable alkyl chloride, the ester being recovered.

(5) The phosphite residue was obtained as a viscous liquid (21·60 g. Calc. for $C_{42}H_{39}O_3P$: 20·70 g.) by heating the reagents to 40—50°/0·1 mm. with automatic shaking (1 hr.). After further heating (80°/0·1 mm. for 1 hr.) the phosphite residue had n_D^{26} 1·5870 (Found: P, 4·80. Calc. for $C_{42}H_{39}O_3P$: P, 5·0%). Distillation of a portion (4·15 g.) caused vigorous decomposition at 165°/0·0005 mm. to a white solid (2·90 g.) which after two recrystallisation from ligroin gave stilbene, m. p. 122—124° (Found: C, 93·1; H, 6·8. Calc. for $C_{14}H_{12}$: C, 93·3; H, 6·7%).

(6) The phosphite residue (11·70 g.) afforded fractions: (i) (4·93 g.), b. p. 160—175°/0·08 mm., n_D^{18} 1·5680; (ii) (5·0 g.), b. p. 185°/0·02 mm., n_D^{14} 1·5749 (Found: C, 71·1; H, 5·8. Calc. for $C_{21}H_{21}O_3P$: C, 71·6; H, 6·0%).

(7) The phosphite residue, after being heated to 40—60°/0·10 mm. (1 hr.) with automatic shaking, had n_D^{21} 1·5440, d_4^0 1·117 (Found: P, 7·82. Calc. for $C_{24}H_{27}O_3P$: P, 7·87%). Distillation caused decomposition at 120—130°/0·05 mm., affording styrene, b. p. 33—35°/10 mm., n_D^{14} 1·5482. A rapid stream of hydrogen chloride was passed into the phosphite residue (5·60 g.) in ether (5 ml.) at −10° for 1 hr. and the excess of gas and ether removed at 15—20 mm. without heating. The product was directly distilled at 0·1 mm. into a trap at −80°. The condensate gave 1-chloro-1-phenylethane (5·60 g., 94% based on 3 groups), b. p. 69°/10 mm., n_D^{16} 1·5300 (Found: Cl, 24·5. Calc. for C_8H_9Cl: Cl, 25·3%). The residue was heated to 100—150°/0·1 mm. for 1 hr. whereupon it weighed 1·25 g. (Found: P, 33·0. Calc. for H_3O_3P: P, 37·8%).

(8) Even at −10° the precipitate was contaminated with phosphite. It was quickly removed from the filter, refluxed with fresh ether, and filtered off. After being dried under vacuum the precipitate was still overweight and had to be twice refluxed with ether and again filtered off. The first filtrate on concentration under reduced pressure yielded a yellow-white, semi-solid substance (8·40 g., 92·5%). Volatile matter was removed at 20°/0·4 mm. (4 hr.) with automatic shaking; the residue weighed 8·20 g. (Found: P, 6·24. Calc. for $C_{36}H_{33}O_3P$: P, 5·70%. Calc. for $C_{24}H_{23}O_3P$: P, 7·95%). All attempts to recrystallise the product failed. Dry hydrogen chloride was passed through a solution of the phosphite residue (2·75 g.) in ether (10 ml.) for 1 hr. at −10°. Volatile matter was removed at 10—15°/10 mm. and, after treatment with water, distillation afforded 1-chloro-1-2′-naphthylethane (2·20 g., 76·3% based on 3 groups), b. p. 82°/0·03 mm. (Found: Cl, 18·6. Calc. for $C_{12}H_{11}Cl$: Cl, 18·6%), and a residue (0·25 g.).

(9) The phosphite residue, after 2 hr. at 20—25°/0·1 mm. (with automatic shaking), was obtained as a waxy solid (19·80 g. Calc. for $C_{39}H_{33}O_3P$: 19·30 g.), m. p. 65—66° (Found: P, 5·21. Calc. for $C_{39}H_{33}O_3P$: P, 5·35%). The phosphite residue (5·40 g.) was suspended in ether (15 ml.), and hydrogen chloride passed in for 1 hr. at −10°. Volatile matter was removed at 15 mm. The clear solution had separated into two layers. The lower layer of phosphorous acid was heated to 100°/0·1 mm. for 1 hr. (Wt., 0·70 g. Calc. for H_3O_3P: 0·77 g.) (Found: P, 32·5. Calc.: P, 37·8%). The upper layer was redissolved in ether and washed. Chlorodiphenylmethane (5·15 g.; 91·2%, 3 groups), b. p. 88—90°/0·05 mm., n_D^{20} 1·5962 (Found: Cl, 17·3. Calc. for $C_{13}H_{11}Cl$: Cl, 17·5%), was obtained.

Phosphorus Oxychloride, Alcohol, and Pyridine.—The alcohol (1 mol.) was weighed into a reaction vessel designed so that the filtration could be accomplished without exposure to air. Pyridine (1·58 g., 1 mol.) in ether (10 ml.) was added, and phosphorus oxychloride (1·03 g., 0·33 mol.) in ether (10 ml.) was then added at −10° (10 min.). After 23 hr. the precipitate was separated, and the filtrate kept for a further 24 hr. and tested for further precipitation. Results are given in Table 3.

TABLE 3.

		Precipitate				
Alcohol no.	Alcohol, g.	Wt., g.	Cl, %, Found	C_5H_5N, %, Found	2nd Ppt., g.	Cl, %, Found
1	2·44	2·28	31·0	68·2	0·10	—
2	2·72	2·30	30·4	67·0	0·10	—
3	4·24	1·60	30·6	67·5	0·42	30·0
4	2·72	1·70	29·8	66·5	0·41	30·6
5	3·96	4·40	14·7	40·5	0·05	—
6	2·16	3·07	14·2	36·8	—	—
8	3·44	3·02	14·1	38·4	—	—
9	3·68	3·90	11·9	26·4	—	—
	Calc. for C_5H_5N,HCl:	2·31	30·7	68·4	—	—

Phosphorus oxychloride (0·034 mole) in ether (10 ml.) was added dropwise to a solution of the alcohol (0·10 mole) and pyridine (0·10 mole) in ether (100 ml.) at −10° (10 min.), and the mixture kept at room temperature for the time stated before filtration. The results are summarised in Table 4, and in the notes.

TABLE 4.

							Distribution of Cl and P, %			
							Cl		P	
Alcohol no.	Time	ROH, g.	Ppt. g.	Analysis of ppt., % Cl	C_5H_5N	P	in ppt.	in filt.	in ppt.	in filt.
1	8 days	12·20	10·88	30·2	67·6	—	92·7	—	—	100
2	9 ,,	13·6	10·75	30·4	68·0	—	92·2	—	—	100
3	24 ,,	21·2	10·44	30·5	68·2	—	90·0	7·0	—	100
4	21 ,,	13·6	10·85	30·2	67·5	—	92·5	—	—	100
5	18 hr.	19·8	14·02	19·4	47·5	7·3	75·2	23·2	97·5	2·3
6	16 ,,	10·8	14·82	15·6	37·2	6·5	64·0	26·0	92·0	7·6
7	16 ,,	12·2	12·47	16·6	44·6	7·4	57·3	—	88·0	12·0
8	18 ,,	17·2	14·05	16·8	38·1	7·5	65·4	33·9	100	—
9	18 ,,	18·4	19·00	15·1	30·5	5·5	79·4	20·4	100	—
	Calc. for C_5H_5N,HCl:	11·55	30·7	68·4	0·0	—	—	—	—	

(1) Distillation of the filtrate gave *tri*-(2-*phenylethyl*) *phosphate* (77% yield), b. p. 192—194°/0·005 mm., n_D^{24} 1·5498, d_4^{20} 1·148 (Found: P, 7·65. $C_{24}H_{27}O_4P$ requires P, 7·56%), and a viscous residue (1·38 g.).

(2) *Tri*-(3-*phenylpropyl*) *phosphate* (62%), b. p. 220°/0·001 mm., n_D^{24} 1·5404, d_4^{20} 1·103 (Found: P, 6·72. $C_{27}H_{33}O_4P$ requires P, 6·85%), and a residue (1·76 g.) were obtained.

(3) The washed and dried filtrate residue (85°/0·1 mm.; 1 hr.) weighed 11·25 g. (Calc. for phosphate: 11·33 g.) (Found: Cl, 2·2; P, 4·74. Calc. for $C_{30}H_{30}O_3ClP$: Cl, 7·0; P, 6·2. Calc. for $C_{45}H_{45}O_4P$: P, 4·6%). The aqueous washings contained chloride ion (0·016 g.) and pyridine (0·115 g.). In this example, approach to the final precipitation of all chlorine and pyridine was very slow.

(4) The primary filtrate (ppt., 10·45 g.) deposited hydrochloride (0·40 g.) during 6 days at 15° and, on being concentrated, gave more precipitate (0·4 g.) (Found: Cl, 30·5%). The

filtrate residue (80°/0·1 mm.; 1 hr.) weighed 14·85 g. (Calc.: 15·05 g.). After being washed and dried, a viscous residue, $[\alpha]_D^{25}$ +21·60° (in $CHCl_3$) (Found: P, 8·0. Calc. for $C_{27}H_{33}O_4P$: P, 6·85%), was obtained. The phosphate (4·40 g.) was heated with aqueous ethanolic potassium hydroxide (50 c.c.; 20%) at 90° for 31 hr., and steamed-distilled (3 hr.) to afford the alcohol (0·80 g.), b. p. 112—114°/23 mm., n_D^{28} 1·5200, α_D^{32} +21·60° (l = 1) (the original alcohol had α_D^{16} +26·72°). The extreme slowness of the hydrolysis and the steric course are in accord with similar observations by Gerrard, Green, and Nutkins (*J.*, 1952, 4076). The phosphate decomposed at 120°/0·5 mm.

(5) The washed and dried filtrate residue, b. p. 60°/0·1 mm., weighed 17·7 g. (Found: Cl, 4·75; P, 0·14%). When the primary reaction mixture (half quantities) was stored for 11 days at room temperature, the precipitate weighed 6·27 g. (Found: Cl, 17·8; P, 6·7; C_5H_5N, 49·0%) and the filtrate residue (60°/0·1 mm.; 1 hr.) weighed 9·60 g. (Found: Cl, 4·00%; P, nil).

(6) The filtrate was directly distilled; impure benzyl chloride (fractionation tedious) (3·30 g.), b. p. 79—81°/23 mm. [large middle cut, b. p. 71—72°/19 mm., n_D^{19} 1·5384 (Found: Cl, 27·7. Calc. for C_7H_7Cl: Cl, 28·0%)], benzyl alcohol (1·55 g.), b. p. 108—109°/23 mm., and a residue (2·85 g.) (Found: P, 2·81%) were obtained.

(7) From the filtrate, volatile matter was removed, first at 15°/20 mm. (residue 12·0 g.), then at 20—80°/0·05 mm. (trap at −80°); the residue (Found: P, 8·52. Calc. for $C_{24}H_{27}O_4P$: P, 7·56%) weighed 1·50 g. The condensate (trap, 10·20 g.) had a wide boiling range and comprised pyridine, 1-chloro-1-phenylethane, and 1-phenylethanol. The speed of the reaction is indicated by the fact that the alcohol (6·1 g.) gave the precipitate (6·08 g.) (Found: Cl, 17·5; P, 8·28; C_5H_5N, 46·3%) when the oxychloride was added very slowly (20 min.) and the mixture allowed to warm to 25° (1 hr.).

(8) The filtrate residue (14·5 g.) (80°/0·1 mm.; 1 hr.) gave a solid (10·0 g.), b. p. 65—80°/0·001—0·01 mm., and a gummy residue (4·40 g.). The solid gave 1-chloro-1-2′-naphthylethane (3·55 g.), b. p. 84—88°/0·1 mm., m. p. 65—66° (from light petroleum (Found: Cl, 18·6. Calc. for $C_{12}H_{11}Cl$: Cl, 18·6%), a liquid (3·40 g.), b. p. 94—96°/0·1 mm., m. p. 52—53° (from light petroleum) (Found: Cl, 9·7%), which appeared to be a mixture of the alkyl chloride and 2-naphthylethylene, and a residue of polymeric gum (2·20 g.).

(9) The filtrate residue (12·1 g.) (Found: Cl, 6·1%) gave a fraction (4·70 g.), b. p. 75—78°/0·002 mm., further resolved into impure alkyl chloride, b. p. 86—88°/0·05 mm. (Found: Cl, 15·2%), and diphenylmethyl chloride, b. p. 88—92°/0·05 mm., n_D^{20} 1·5962 (Found: Cl, 17·4. Calc. for $C_{13}H_{11}Cl$: Cl, 17·5%). A viscous residue (6·30 g.) afforded bisdiphenylmethyl ether (5·10 g., 29·1%), b. p. 170°/0·03 mm., m. p. 107—108°, mixed m. p. 107—108°.

Materials.—All reagents were carefully purified before use; solvents were dried. 1-Phenylpropan-2-ol was obtained by reduction of the ketone with sodium and ethanol (Pickard and Kenyon, *J.*, 1911, **99**, 58; 1913, **103**, 1943) and was resolved by the method of these workers (*J.*, 1914, **107**, 1115). 1:3-Diphenylpropan-2-ol was similarly obtained from the ketone, and 1-2′-naphthylethanol was obtained from the ketone by reduction with aluminium *iso*propoxide (Arcus and Kenyon, *J.*, 1938, 698). 1:2-Diphenylethanol was obtained as described by Gerrard and Kenyon (*J.*, 1928, 2564).

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423. *Reactions of Fluorocarbon Radicals. Part X.* Polyfluoroalkyl Nitroso- and Nitro-compounds.*

By R. N. Haszeldine.

Nitric oxide combines with the perfluoroalkyl radicals $CF_3{\cdot}[CF_2]_n{\cdot}$ produced photochemically from the corresponding perfluoroalkyl iodides, to give the intensely blue, monomeric nitroso-compounds $CF_3{\cdot}[CF_2]_n{\cdot}NO$ (n = 1, 2, 3, 4, or 6). The compounds $CClF_2{\cdot}CF_2{\cdot}NO$, $CBrF_2{\cdot}CF_2{\cdot}NO$, $CBrF_2{\cdot}NO$, $CClF_2{\cdot}NO$, and $(C_2F_5)(CF_3)CF{\cdot}NO$ are similarly obtained. Oxidation of the corresponding nitroso-compounds yields $CF_3{\cdot}NO_2$, $C_2F_5{\cdot}NO_2$, $C_3F_7{\cdot}NO_2$, and $CClF_2{\cdot}NO_2$. The compounds $CClF_2{\cdot}CF_2{\cdot}NO_2$, $CClF_2{\cdot}CClF{\cdot}NO_2$, and $CClF_2{\cdot}CCl_2{\cdot}NO_2$ are obtained by the reaction of nitrosyl chloride with tetrafluoroethylene, chlorotrifluoroethylene, and 1 : 1-dichlorodifluoroethylene, respectively; nitrosyl bromide and tetrafluoroethylene similarly yield 1-bromotetrafluoro-2-nitroethane. 1-Chlorotetrafluoro-2-nitroethane can also be obtained from tetrafluoroethylene and nitryl chloride. Nitrogen dioxide readily combines with $CClF{:}CF_2$, $CCl_2{:}CF_2$, or C_2F_4 to give the corresponding dinitro-compounds. Attempts to replace the chlorine or bromine in $CClF_2{\cdot}NO_2$ or $CBrF_2{\cdot}CF_2{\cdot}NO_2$ by fluorine lead mainly to carbon–nitrogen bond fission.

This paper records the beginning of an investigation initiated some years ago into the preparation and properties of polyfluoro-compounds containing nitrogen, and is concerned with polyhalogeno-nitroso- and -nitro-alkanes.

Ruff and Giese (*Ber.*, 1936, **69**, 598, 684) obtained a low yield of a blue gas when silver cyanide was treated with fluorine, and concluded that it was trifluoronitrosomethane, and that the oxygen it contained arose from the silver nitrate present as impurity. The trifluoronitrosomethane was contaminated with a colourless gas from which it could not be separated, and from a series of qualitative reactions Ruff and Giese concluded that the colourless very stable compound was $F{\cdot}CO{\cdot}NF_2$. Trifluoronitrosomethane was believed to isomerise to the trifluoroformamide :

$$CF_3{\cdot}NO\ (\text{blue};\ \text{b. p. } -84^\circ;\ \text{f. p. } -196{\cdot}6^\circ) \longrightarrow F{\cdot}CO{\cdot}NF_2\ (\text{colourless};\ \text{b. p. } -82{\cdot}4^\circ;\ \text{f. p. } -152{\cdot}2^\circ)$$

Pure trifluoronitrosomethane has now been obtained by irradiation of a mixture of trifluoroiodomethane and nitric oxide in the presence of mercury, which removes the iodine atom liberated and combines with any nitrogen dioxide formed :

$$CF_3I \xrightarrow{h\nu,\ Hg} CF_3{\cdot} \xrightarrow{NO} CF_3{\cdot}NO$$

The nitroso-compound is a gas with a magnificent deep blue colour, and on cooling yields a deep blue liquid and purple solid. Its ultra-violet and infra-red spectra have been recorded and, with a study of the rearrangement postulated by Ruff and Giese, will be reported by Dr. J. Jander.

Extension of the above method to the homologues of trifluoroiodomethane described earlier (*J.*, 1949, 2856; *J.*, 1952, 4259; *Nature*, 1950, **166**, 192) gave the blue compounds $CF_3{\cdot}[CF_2]_n{\cdot}NO$ (n = 1, 2, 3, 4, or 6) in low conversion but high yield (cf. *ibid.*, 1951, **168**, 1028). Molecular-weight determinations show that the compounds are not associated, and this agrees with the Trouton constant of 21·2 recorded for trifluoronitrosomethane by Ruff and Giese (*loc. cit.*). The synthetic method is of general application, and the fluoroiodides $CClF_2{\cdot}CIF_2$, $CBrF_2{\cdot}CIF_2$, $CBrIF_2$, and $CClIF_2$ gave the corresponding nitroso-compounds. The first two of these fluoro-iodides were prepared from tetrafluoroethylene by reaction with iodine mono-chloride or -bromide. A secondary perfluoroalkyl-nitroso-compound was also prepared [$(C_2F_5)(CF_3)CF{\cdot}NO$].

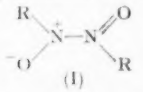
Few alkyl nitroso-compounds are monomeric under normal conditions, and four main types may now be distinguished : (*a*) Those which contain the >CH·NO group form

* Part IX, *J.*, 1953, 1548.

colourless dimers or isomerise to the oxime >C:N·OH (*e.g.*, MeNO; Coe and Doumani, *J. Amer. Chem. Soc.*, 1948, **70**, 1516). (*b*) Those which contain hydrogen and halogen on the α-carbon atom isomerise only slowly, but form colourless dimers :

$$CHRX{\cdot}NO \longrightarrow CRX{:}N{\cdot}OH \text{ or } (CHRX{\cdot}NO)_2;\ X = Cl, Br.$$

(*c*) Those which contain the nitroso-group attached to a tertiary carbon atom cannot isomerise, but yield colourless dimers [*e.g.*, $(Me_3C{\cdot}NO)_2$]. The colourless dimers of (*b*) and (*c*) often partly dissociate to the blue monomer when heated or melted, or dissolved in an organic solvent, and their structures can be represented by resonance forms of type (I) (Fenimore, *ibid.*, 1950, **72**, 3226; Darwin and Hodgkin, *Nature*, 1950, **166**, 827). (*d*) The



(I)

polyfluoro-nitroso-compounds, which do not form dimers under normal conditions. This is attributed to the powerful inductive effect of the polyfluoroalkyl group which reduces the availability for bond formation of the lone pair of electrons of the nitrogen atom in the nitroso-compounds and so prevents dimer formation of type (I). The absence of basic character in the fluoro-amines [*e.g.*, $N(CF_3)_3$, $FN(CF_3)_2$] is another example of this effect (Haszeldine, *J.*, 1951, 102; *Research*, 1951, **4**, 338). The compounds $CMe_2X{\cdot}NO$ (X = Cl or Br) exist mainly in the blue monomeric form (Piloty, *Ber.*, 1898, **31**, 452).

Perfluoronitroalkanes were required for studies on perfluoroalkylamines, but application of the usual synthetic methods (*e.g.*, reaction with silver nitrite) to the corresponding iodo-compounds failed (Banus, Emeléus, and Haszeldine, *J.*, 1951, 60). Four alternative methods have been devised : (*a*) Oxidation of the nitroso-compounds. (*b*), (*c*), and (*d*) Reaction of nitrosyl chloride, nitryl chloride, or nitrogen dioxide with fluoro-olefins.

Treatment of the appropriate nitroso-compound with dimanganese heptoxide, lead dioxide, or chromic oxide gave the compounds $CF_3{\cdot}NO_2$ (fluoropicrin), $C_2F_5{\cdot}NO_2$, $C_3F_7{\cdot}NO_2$, and $CClF_2{\cdot}NO_2$. Their boiling points are compared with those of related compounds in Table 1. It is noteworthy that dichloro- and trichloro-nitromethane have similar boiling

TABLE 1. *Boiling points.*

	$MeNO_2$ 101°		$EtNO_2$ 115°		$PrNO_2$ 132°	
$CCl_3{\cdot}NO_2$	112°	$CH_2Cl{\cdot}NO_2$ ..... 123°	$CF_3{\cdot}CH_2{\cdot}NO_2$ ...	96° [2]	$CF_3{\cdot}(CH_2)_2{\cdot}NO_2$	135° [1,2]
$CClF_2{\cdot}NO_2$ ...	25	$CHCl_2{\cdot}NO_2$ 107	$C_2F_5{\cdot}NO_2$	0	$C_3F_7{\cdot}NO_2$	25
$CF_3{\cdot}NO_2$	−20	$CCl_3{\cdot}NO_2$ 112				

[1] Schechter and Conrad, *J. Amer. Chem. Soc.*, 1950, **72**, 3371. [2] McBee, Hass, and Robinson, *ibid.*, p. 3579.

points which are only slightly higher than that of the unsubstituted compound, despite the marked increase in molecular weight (cf. $CH_3{\cdot}CO_2H$, b. p. 118°; $CCl_3{\cdot}CO_2H$, b. p. 197°). Comparison of $EtNO_2$, $CF_3{\cdot}CH_2{\cdot}NO_2$, and $C_2F_5{\cdot}NO_2$ shows that replacement of hydrogen by fluorine on the α-carbon atom causes a very large decrease in boiling point, and this can be related to the inductive effect of the group attached to the readily polarised NO_2 group (cf. the nitriles : $CH_3{\cdot}CN$, b. p. 82°; $CF_3{\cdot}CN$, b. p. −64°).

Ruff and Giese (*loc. cit.*) reported that their blue compound failed to react with chromic oxide, and Hückel (*Nach. Ges. Wiss. Göttingen*, 1946, **36**; *Chem. Abs.*, 1949, **43**, 6793) in a preliminary note reported that lead dioxide oxidised the nitroso-compound, but did not describe the properties of the product.

Chlorodifluoronitromethane gave mainly chlorotrifluoromethane when heated with antimony trifluorodichloride, *i.e.*, fission of the carbon–nitrogen bond occurred in preference to replacement of chlorine by fluorine :

$$CClF_2{\cdot}NO_2 \xrightarrow{SbF_3Cl_2} CClF_3 + NO_2F$$

Pyrolysis of trifluoronitromethane in a platinum tube did not produce carbon tetrafluoride, hexafluoroethane, tetrafluoroethylene, or perfluoro*cyclo*butane, but gave a mixture which was probably nitrosyl fluoride, carbon dioxide, and carbonyl fluoride, *i.e.*, $CF_3{\cdot}NO_2 \longrightarrow NOF + COF_2$. Pyrolysis in a silica apparatus gave only silicon tetrafluoride, carbon dioxide, and oxides of nitrogen. Perfluoronitropropane gave similar products when

pyrolysed in platinum, but also yielded small amounts of hexafluoropropene and pentafluoropropionyl fluoride :

$$C_3F_7{\cdot}NO_2 \longrightarrow NOF + C_2F_5{\cdot}COF, \text{ or } C_3F_7{\cdot}NO_2 \longrightarrow C_3F_7{\cdot} \xrightarrow{NO_2} C_2F_5{\cdot}COF$$
$$C_3F_7{\cdot}NO_2 \longrightarrow C_3F_6 + NO_2F$$

The main product of the reaction of nitrosyl chloride with a fluoro-ethylene is the nitro-compound, *i.e.*, the addition reaction is followed by oxidation :

$$CF_2{:}CXY \xrightarrow{NOCl} CClF_2{\cdot}CXY{\cdot}NO \longrightarrow CClF_2{\cdot}CXY{\cdot}NO_2$$

The compounds $CClF_2{\cdot}CF_2{\cdot}NO_2$, $CClF_2{\cdot}CClF{\cdot}NO_2$, and $CClF_2{\cdot}CCl_2{\cdot}NO_2$ were prepared in good yield, and the reaction is not limited to fluoro-olefins, since trichloroethylene gave 1 : 1 : 1 : 2-tetrachloro-2-nitroethane. It is assumed that nitrosyl chloride reacts as NO^+Cl^- and not by a free-radical mechanism, and that the direction of addition to the fluoro-olefin is the same as in other reactions involving ionic intermediates (*e.g.*, iodine monochloride, Haszeldine, *J.*, 1952, 4423; alcohols and amines, Miller, Fager, and Griswold, *J. Amer. Chem. Soc.*, 1948, **70**, 431), where the negative substituent becomes attached to the CF_2 group of the olefin. Evidence for the constitution of the nitro-compound from trichloroethylene is the formation of trichloroacetic acid on treatment with concentrated sulphuric acid. The reaction of nitrosyl bromide with tetrafluoroethylene similarly yielded 1-bromotetrafluoro-2-nitroethane.

Infra-red spectroscopic studies reported in another series show that the NO_2 group in aliphatic compounds is characterised by its asymmetric and symmetric stretching vibrations (*ca.* 6·45 and 7·24—7·35 μ), and that when a powerful electron-attracting group [*e.g.*, CBr_3, CCl_3, $C(NO_2)_3$] is attached directly to the NO_2 group these bands shift to shorter and longer wave-length respectively (6·18—6·28 μ; 7·65—7·85 μ). The infra-red spectrum of 1-chlorotetrafluoro-2-nitroethane shows strong absorption at 6·18 and 7·85 μ which supports its formulation as a nitro-compound, as distinct from the isomeric nitrite. Its ultra-violet spectrum shows a maximum which is characteristic for nitro-compounds containing halogen on the α-carbon atom (see Table 2).

TABLE 2. *Ultra-violet spectra in light petroleum.*

	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$	$\lambda_{min.}$	$\varepsilon_{min.}$
$Pr^n{\cdot}NO_2$	280	23	247	10
$CHEtCl{\cdot}NO_2$	283·5	28	249	13·5
$CMe_2Cl{\cdot}NO_2$	283·5	28	248·5	8
$CClF_2{\cdot}CF_2{\cdot}NO_2$ (vapour)	282·5	48	236·5	5·8
$CCl_3{\cdot}NO_2$	278·5	52	247·5	16

Attempts were made to replace the bromine in 1-bromotetrafluoro-2-nitroethane by fluorine, and so provide a general route to the synthesis of perfluoronitroalkanes from the olefins :

$$CF_2{:}CX_2 \longrightarrow CBrF_2{\cdot}CX_2{\cdot}NO_2 \longrightarrow CF_3{\cdot}CX_2{\cdot}NO_2$$

where X = F, perfluoroalkyl, perfluoro*cyclo*alkyl, etc. Reaction with bromine trifluoride gave only a low yield of perfluoronitroethane, however, and the main product was bromopentafluoroethane. Antimony trifluorodichloride also caused carbon–nitrogen bond fission to yield bromopentafluoroethane, and perfluoronitroethane was not isolated. The formation of chlorotrifluoromethane from the attempted replacement of chlorine by fluorine in $CClF_2{\cdot}NO_2$ has been described above.

The third method for the preparation of polyfluoronitroalkanes involves the reaction of nitryl chloride with the fluoro-olefin : tetrafluoroethylene gave 1-chlorotetrafluoro-2-nitroethane identical with the material from nitrosyl chloride :

$$C_2F_4 \xrightarrow{NO_2Cl} CClF_2{\cdot}CF_2{\cdot}NO_2$$

The reaction of nitrogen dioxide with polyhalogeno-olefins (Biltz, *Ber.*, 1902, **35**, 1528; Argo, James, and Donnelly, *J. Phys. Chem.*, 1919, **23**, 578; Coffman *et al.*, *J. Org. Chem.*, 1949, **14**, 747) has now been extended to chlorotrifluoroethylene, 1 : 1-dichloro-

difluoroethylene, and tetrafluoroethylene, and found to yield the corresponding dinitro-compounds :

$$CF_2{:}CX_2 \xrightarrow{NO_2} NO_2{\cdot}CF_2{\cdot}CX_2{\cdot}NO_2$$

The above reactions thus give compounds of the general type RX being studied in this series of papers, where R is a polyfluoro-group and X is a potentially reactive group (see *J.*, 1951, 588). The influence of the strongly electronegative R on the properties of X (NO or NO_2) is being investigated.

Experimental

The nitrogen compounds described below may be lachrymators and have been manipulated in a vacuum-system wherever possible.

Preparation of Fluoro-iodides.—The perfluoroalkyl iodides were prepared by the reaction of iodine with the silver salt of the appropriate acid (*J.*, 1952, 4259), or by the interaction of trifluoroiodomethane or pentafluoroiodoethane and tetrafluoroethylene (*Nature*, 1950, **166**, 192). Nonafluoro-2-iodobutane was obtained by the photochemical reaction of trifluoroiodomethane with hexafluoropropene (Haszeldine and Steele, Amer. Chem. Soc. Meeting, Atlantic City, 1952).

Chlorodifluoroiodomethane and bromodifluoroiodomethane were prepared as earlier (*J.*, 1952, 4259).

Tetrafluoroethylene (2·0 g.), sealed in a 50-ml. Pyrex tube with a 10% excess of iodine monochloride and slowly heated to 50°, gave, after washing with 10% aqueous sodium hydroxide to remove traces of iodine, drying (P_2O_5), and distillation, 1-*chlorotetrafluoro*-2-*iodoethane* (94%), a colourless liquid, b. p. 56·5°, $n_D^{18\cdot5}$ 1·393 (Found : C, 8·9%; *M*, 261. C_2ClF_4I requires C, 9·1%; *M*, 262·5).

Interaction of tetrafluoroethylene (2·0 g.) and iodine monobromide (10% excess), at a maximum temperature of 80°, similarly yielded 1-*bromotetrafluoro*-2-*iodoethane* (90%), b. p. 80·5—81·0°, n_D^{16} 1·433 (Found : C, 8·0%; *M*, 307. C_2BrF_4I requires C, 7·8%; *M*, 307).

Ultra-violet spectra : $CClF_2{\cdot}CIF_2$ (vapour) $\lambda_{max.}$ 269 mμ (ε 245), $\lambda_{min.}$ 220 (ε 24); (light petroleum solution) $\lambda_{max.}$ 272 (ε 295), $\lambda_{min.}$ 215 (ε 17). $CBrF_2{\cdot}CIF_2$ (vapour) $\lambda_{max.}$ 269·5 (ε 343), $\lambda_{min.}$ 237·5 (ε 125); (light petroleum solution) $\lambda_{max.}$ 273 (ε 385), $\lambda_{min.}$ 236 (ε 140).

Nitric oxide, nitrogen dioxide, nitrosyl chloride, and nitrosyl bromide were purified by distillation through a packed column, or by fractional condensation in a vacuum-system, and were transferred to the reaction vessel *in vacuo*.

Polyhalogenoalkyl Nitroso-compounds.—The following general procedure was adopted for the preparation of the nitroso-compounds: The fluoro-, fluorochloro-, or fluorobromo-iodide (0·01—0·02 mole, depending on its volatility) was sealed in a 100-ml. silica tube with mercury (20—30 ml.) and nitric oxide (0·02—0·04 mole). The tube was shaken vigorously in a horizontal position in a vibro-shaker, and irradiated by a Hanovia S 250 lamp at 5—10 cm. distance; intimate mixing of the liquid and vapour with mercury was essential for good yields. After irradiation for 6—7 hr., a blue colour could be seen in the vapour or liquid phase. Irradiation was continued for 3—7 days, and the contents of the tube were fractionated *in vacuo* to remove the excess of nitric oxide. Final purification was achieved as follows. Compounds of b. p. >40°: distillation through a semimicro-column in an atmosphere of nitrogen and under reduced pressure to prevent possible isomerisation by excessive heating. Compounds of b. p. <40°: fractionation in a vacuum-system followed by treatment with ice-cold dilute aqueous alkali for 2—3 min. and refractionation. Special treatment was necessary for trifluoronitrosomethane which cannot be freed from excess of nitric oxide by distillation in a vacuum-system : air or oxygen was admitted into a bulb containing the crude nitroso-compound, and the nitrogen dioxide so formed was separated by further fractionation. Final purification was effected by shaking the nitroso-compound with ice-cold 2% sodium hydroxide solution in a sealed tube for 3—5 min. to remove traces of oxides of nitrogen, carbon dixoide, and carbonyl fluoride, followed by repeated fractionation *in vacuo*.

The deep blue *compounds* so prepared are given in Table 3, and apart from trifluoronitrosomethane (Ruff and Giese, *loc. cit.*) are new. The yield is based on the iodo-compound used, and the yield based on the iodo-compound taken is shown in parentheses. For carbon analysis, the compounds were pyrolysed in a stream of oxygen over silver vanadate at 700°; nitrogen analysis was effected in the usual way. Molecular weights were determined by Regnault's method, and the b. p. of a middle cut of a particular fraction was measured in an isoteniscope.

Addition of Nitrosyl Chloride to Halogeno-olefins.—(a) *Tetrafluoroethylene.* Nitrosyl chloride (13·2 g., 0·2 mole) was sealed *in vacuo* in a 200-ml. Pyrex tube with tetrafluoroethylene (5·0 g., 0·05 mole) and slowly heated to 50°. On cooling, it was noted that the volume of the liquid phase had increased. The tube was cooled in liquid nitrogen, then opened, and more tetrafluoroethylene was added (4·0 g., 0·04 mole); after reheating and cooling, the contents of the reaction vessel were fractionated *in vacuo* to remove unchanged nitrosyl chloride and then

TABLE 3. *Nitroso-compounds.*

Compound	B. p.	Yield (%)	Found C, %	Found N, %	Found *M*	Required C, %	Required N, %	Required *M*
CF_3·NO	−84° [1]	75 (10)	—	14·0	99	—	14·2	99
C_2F_5·NO	−42	80 (10)	16·4	9·0	150	16·1	9·4	149
C_3F_7·NO	−12	83 (16)	18·4	6·9	199	18·1	7·0	199
C_4F_9·NO	16—17°/730 mm.	81 (8)	19·5	5·5	249	19·3	5·6	249
C_5F_{11}·NO	19—20°/230 mm. (50°/760 mm., micro)	71 (12)	20·0	—	298	20·1	4·7	299
C_7F_{15}·NO	39—40°/63 mm. (95°/760 mm., micro)	75 (14)	21·1	3·4	400	21·0	3·5	399
$(C_2F_5)(CF_3)CF$·NO	23—25°	86 (23)	19·0	5·8	249	19·3	5·6	249
$CClF_2$·CF_2·NO	−2	68 (11)	14·4	8·3	165	14·5	8·5	165·5
$CBrF_2$·CF_2·NO	18	52 (10)	—	6·6	210	11·4	6·7	210
$CBrF_2$·NO	*ca.* −12 [2]	50 (10)	7·8	8·8	160	7·5	8·7	160
$CClF_2$·NO	*ca.* −35 [2]	50 (10)	10·6	12·4	114	10·4	12·1	115·5

[1] B. p. given by Ruff and Giese, *loc. cit.* [2] B. p. approximate, since the compound was difficult to purify with the amount available; experiments on one-quarter of the usual scale.

distilled to give 1-*chlorotetrafluoro*-2-*nitroethane* (63%), b. p. 36—37°, n_D^{22} 1·3145 (Found: C, 12·9; N, 7·7%; *M*, 181. $C_2O_2NClF_4$ requires C, 13·2; N, 7·7%; *M*, 181·5), as a colourless liquid. Treatment of the fraction containing residual nitrosyl chloride with aqueous sodium hydroxide left 1 : 2-dichlorotetrafluoroethane (8%), b. p. 4° (Found: *M*, 170. Calc. for $C_2Cl_2F_4$: *M*, 171).

(b) *Chlorotrifluoroethylene.* The procedure of (a) was applied to chlorotrifluoroethylene (0·10 mole) and nitrosyl chloride (0·23 mole), with a final reaction temperature of 100°. The material of b. p. <30° was removed by vacuum-fractionation, and the residual material was washed with water, dried (P_2O_5), and distilled, to give 1 : 2-*dichlorotrifluoro*-2-*nitroethane* (67%), b. p. 75—76° (Found: C, 12·1; N, 7·3%; *M*, 198. $C_2O_2NCl_2F_3$ requires C, 12·1; N, 7·1%; *M*, 198), and 1 : 1 : 2-trichlorotrifluoroethane (16%), b. p. 46—48° (Found: *M*, 187. Calc. for $C_2Cl_3F_3$: *M*, 187·5).

(c) 1 : 1-*Dichlorodifluoroethylene.* This compound (0·06 mole) and nitrosyl chloride (0·15 mole), treated as in (b) above, gave 1 : 1 : 2-*trichlorodifluoro*-1-*nitroethane* (57%), b. p. 72—73°/151 mm., 117—118°/760 mm. (micro) (Found: N, 6·6; Cl, 49·5; F, 17·5%; *M*, 212. $C_2O_2NCl_3F_2$ requires N, 6·5; Cl, 49·7; F, 17·7%; *M*, 214·5), and 1 : 1-difluorotetrachloroethane (18%), b. p. 91—92°.

The still-residues from experiments (a), (b), and (c) above probably contain organic nitrates.

(d) *Trichloroethylene.* Trichloroethylene (5·0 g.) was heated with an excess of nitrosyl chloride (6·5 g.) at 100° for 2 hr., to give, after distillation in an atmosphere of nitrogen after washing with water and drying (P_2O_5), unchanged trichloroethylene (0·5 g.), pentachloroethane (1·1 g.), b. p. 158—160°, and 1 : 1 : 1 : 2-*tetrachloro*-2-*nitroethane* (62%), b. p. 95—96°/40 mm. (Found: N, 6·6; Cl, 66·4. $C_2HO_2NCl_4$ requires N, 6·6; Cl, 66·7%). A 2-g. sample of the last product was added dropwise to ice-cold concentrated sulphuric acid (10 ml.), the mixture was heated under reflux for 1 hr., and the product was removed *in vacuo*. Redistillation gave trichloroacetic acid (52%).

Interaction of Nitrosyl Bromide and Tetrafluoroethylene.—Nitrosyl bromide (3·3 g.; prepared from nitric oxide and bromine) was sealed with tetrafluoroethylene (2·0 g.) and kept at 0° for 1 week, then heated to 55° during 4 hr. The product was distilled rapidly in a vacuum-system to remove nitrosyl bromide, etc., and the crude residual product was washed once with ice-water, dried (P_2O_5), and distilled, to give 1-*bromotetrafluoro*-2-*nitroethane* (37%), b. p. 56—58° (Found: N, 6·0; Br, 35·6%; *M*, 222, 224. $C_2O_2NBrF_4$ requires N, 6·2; Br, 35·4%; *M*, 226), 1 : 2-dibromotetrafluoroethane (*ca.* 10%), b. p. 44—46°, and unidentified products.

Reaction of Nitryl Chloride with Tetrafluoroethylene.—Nitryl chloride was prepared from 100% nitric acid and anhydrous chlorosulphonic acid (Dachlauer, G.P. 509,405/1929), and was purified

by distillation through a short low-temperature column. It had b. p. −16°. Schumacher and Sprenger (*Z. anorg. Chem.*, 1929, **182**, 139) report b. p. −15°.

Tetrafluoroethylene (2·0 g.) was sealed with nitryl chloride (20% excess) and the mixture was allowed to warm slowly to room temperature. After 2 hr. the tube was heated to 60°, then cooled, and the contents were fractionated in a vacuum-system, to give 1-chlorotetrafluoro-2-nitroethane (57%), b. p. 36—38°, identical with the material obtained from nitrosyl chloride and tetrafluoroethylene.

Oxidation of Nitroso- to Nitro-compounds.—(a) *Trifluoronitrosomethane.* Dimanganese heptoxide (*ca.* 1 g.; prepared by dropwise addition of potassium permanganate solution to cold concentrated sulphuric acid, followed by dropwise addition of ice-water, then removal of the brown heptoxide layer) was sealed in a Carius tube with trifluoronitrosomethane (0·3 g.) and slowly allowed to warm to 0°. After 24 hr. in the dark the tube was heated to 25° for 2 hr., then cooled, and the volatile contents were transferred to a vacuum-system. Repeated fractionation gave *trifluoronitromethane* (49%), b. p. −20° (isoteniscope) (Found: C, 10·6; N, 12·4%; *M*, 115. CO_2NF_3 requires C, 10·4; N, 12·2%; *M*, 115). Care must be taken, since several reaction tubes exploded during this reaction.

Use of a solution of dimanganese heptoxide (*ca.* 1·5 g.) in glacial acetic acid (3 ml.) gave a 26% yield of trifluoronitromethane from trifluoronitrosomethane (0·4 g.).

Chromic oxide (1·6 g.), heated to 70° for 10 hr. with trifluoronitrosomethane (0·2 g.), gave trifluoronitromethane (b. p. −21°) in 38% yield. With glacial acetic acid (4 ml.) as solvent, a similar reaction gave a 27% yield of the nitro-compound.

Trifluoronitrosomethane (0·42 g.), sealed with lead dioxide (5·5 g.) and heated to 100° for 48 hr., gave a 37% yield of trifluoronitromethane (b. p. −18°). Yields were not consistent: successive experiments at 20°, 45°, 70°, and 100° gave 32, 15, 8, and 29% yields.

Carbon dioxide, silicon tetrafluoride, and carbonyl fluoride were by-products from the oxidation of trifluoronitrosomethane and, after an initial fractionation in the vacuum-system to remove carbon dioxide, the residual material was shaken twice with ice-water and once, rapidly, with ice-cold 2% aqueous sodium hydroxide. Final purification was effected in the vacuum-system.

(b) *Pentafluoronitroethane and heptafluoronitropropane.* Pentafluoronitrosoethane (0·3 g.), treated with dimanganese heptoxide as in (a) above, gave *pentafluoronitroethane* (33%), b. p. −1° to 0° (isoteniscope) (Found: C, 14·4; N, 8·3%; *M*, 165. $C_2O_2NF_5$ requires C, 14·5; N, 8·5%; *M*, 165). Lead dioxide similarly gave a 30% yield of the nitro-compound (b. p. 0—1°).

Dimanganese heptoxide and heptafluoronitrosopropane (0·5 g.) similarly gave *heptafluoronitropropane* (41%), b. p. 25° (isoteniscope) (Found: C, 16·8; N, 6·6%; *M*, 214. $C_3O_2NF_7$ requires C, 16·7; N, 6·5%; *M*, 215). Lead dioxide gave a 22% yield of the nitro-compound, b. p. 26° (isoteniscope).

(c) *Chlorodifluoronitromethane.* The oxidation of chlorodifluoronitrosomethane (0·2 g.) was difficult to effect without extensive decomposition. Dimanganese heptoxide [(a) above] gave a 15% yield at 20°, and lead dioxide a 10% yield at 75°. The combined crude product was redistilled, to give *chlorodifluoronitromethane*, b. p. 24—25° (isoteniscope) (Found: C, 8·9; N, 10·5; Cl, 26·7%; *M*, 131. CO_2NClF_2 requires C, 9·1; N, 10·6; Cl, 27·0%; *M*, 131·5).

Interaction of Chlorodifluoronitromethane and Antimony Trifluorodichloride.—Antimony trifluoride (5·0 g.) and chlorine (1·5 g.) were heated to 100° for 1 hr. in a small steel autoclave. After cooling, chlorodifluoronitromethane (0·2 g.) was condensed in, and the autoclave was heated to 100° during 6 hr. The volatile reaction products were shaken with cold 2% aqueous sodium hydroxide for 3 min., transferred to a vacuum-system, and fractionated, to give unchanged chlorodifluoronitromethane (*ca.* 10%), chlorotrifluoromethane (53%), and dichlorodifluoromethane (8%). The last two compounds were identified by their infra-red spectra. Trifluoronitromethane could not be detected as a product.

Reaction of 1-Bromotetrafluoro-2-nitroethane with Antimony Trifluorodichloride and with Bromine Trifluoride.—The nitro-compound (0·3 g.) and antimony trifluorodichloride (5·0 g.) heated to 160° for 4 hr. in a small autoclave gave bromopentafluoroethane (41%), b. p. −21°, 1-bromotetrafluoro-2-nitroethane (27%), and a mixture of unidentified products with b. p. $< -30°$, probably containing nitryl and nitrosyl fluorides, carbon dioxide, carbonyl fluoride, etc. Pentafluoronitroethane was not detected.

Bromine trifluoride (4 ml.) in a small autoclave was cooled in liquid nitrogen whilst 1-bromotetrafluoro-2-nitroethane (0·8 g.) was distilled in. The autoclave was sealed and immersed in ice where it was left for 6 hr. It was then vigorously shaken at 20° for 2 hr., and at 50°

for 1 hr. The volatile products were removed, washed with water, and distilled in a vacuum-system, to give pentafluoronitroethane (15%) (see above), bromopentafluoroethane (47%), unchanged bromotetrafluoronitroethane (8%), and unidentified volatile compounds.

Pyrolysis of Trifluoronitromethane and Heptafluoronitropropane.—Trifluoronitromethane (0·5 g.) was allowed to evaporate from a trap and pass through a platinum tube heated to 500° ± 10° over a 9″ length, and the products were collected in a silica trap cooled in liquid nitrogen. Infra-red spectroscopic examination showed that carbon tetrafluoride was not formed. There was no indication of the formation of a polymer of tetrafluoroethylene type, and the products (b. p. <40°) contained a solid (probably carbon dioxide and carbonyl fluoride) which sublimed if the pressure was <700 mm., and a liquid. Approximately half the mixture was sealed with 10% sodium hydroxide solution for 12 hr. Sodium fluoride was precipitated, and no residual gas was detected, *i.e.*, hexafluoroethane, tetrafluoroethylene, perfluoro*cyclo*-butane, etc., were not present. The residual product from the experiment was transferred to a vacuum-system; fractionation showed that most of the mixture had b. p. < −30°, but small amounts of nitrogen dioxide were separated. Attack on the glass was apparent and yielded silicon tetrafluoride and dinitrogen trioxide, thus revealing the presence of nitrosyl fluoride ($SiO_2 + 4NOF \longrightarrow SiF_4 + 2NO + 2NO_2$).

A similar reaction in a silica tube at 450° gave only a mixture of carbonyl fluoride, carbon dioxide, and oxides of nitrogen; fluorocarbon products were not detected.

Heptafluoronitropropane (0·4 g.), pyrolysed in a platinum tube at 500°, gave a similar mixture of products containing nitrosyl fluoride, carbonyl fluoride, and carbon dioxide. Treatment of a portion of the volatile products with an excess of 5% aqueous sodium hydroxide left hexafluoropropene (*ca.* 8%; identified by its infra-red spectrum). The sodium hydroxide solution was filtered, acidified with concentrated sulphuric acid, and extracted with ether. The ethereal extracts were treated with silver carbonate, and filtered, and the ether was removed, leaving silver pentafluoropropionate (19%) (Haszeldine, *J.*, 1952, 4259), identified by its infra-red spectrum.

Addition of Nitrogen Dioxide to Double Bonds.—Chlorotrifluoroethylene (2·9 g.) was sealed with thoroughly dried nitrogen dioxide (4·6 g.) in a small steel autoclave, and slowly heated to 65° (6 hr.). The products were pumped from the autoclave into a trap cooled by liquid nitrogen, rapidly washed once with water, dried (P_2O_5), and distilled, to give 1-*chlorotrifluoro*-1 : 2-*dinitroethane* (51%), b. p. 98·5—100° (Found : C, 11·4; N, 13·6%; *M*, 205, 206. $C_2O_4N_2ClF_3$ requires C, 11·5; N, 13·4%; *M*, 208·5), and unchanged olefin (22%).

1 : 1-Dichlorodifluoroethylene (2·5 g.), similarly treated with nitrogen dioxide (4·0 g.), gave 1 : 1-*dichlorodifluoro*-1 : 2-*dinitroethane* (47%), b. p. 81—82°/103 mm. [micro-b. p. *ca.* 142°/760 mm. (partial decomp.)] (Found : C, 10·6; Cl, 31·0; N, 12·4. $C_2O_4N_2Cl_2F_2$ requires C, 10·7; Cl, 31·6; N, 12·5%).

Tetrafluoroethylene (5·0 g.) and nitrogen dioxide (10·0 g.), sealed and heated to 60° during 8 hr., gave 1 : 1 : 2 : 2-tetrafluorodinitroethane (53%), b. p. 58·5—59° (Found : *M*, 190. Calc. for $C_2O_4N_2F_4$: *M*, 192). Coffman *et al.* (*loc. cit.*) report b. p. 58—59°.

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424. *The Thermal Decomposition of Tetrafluoroethylene.*

By B. Atkinson and A. B. Trenwith.

The thermal decomposition of tetrafluoroethylene at temperatures from 300° to 800° is described. Below 600° dimerization to octafluoro*cyclo*butane, and the reverse reaction, are much faster than any of the other reactions taking place. Hexafluoropropene and octafluorobutenes are formed at 600—800°. At 800° hexafluoroethane and tars are also obtained. Vapour-pressure measurements for the major products are reported.

In the reaction, 2 tetrafluoroethylene $\rightleftharpoons$ octafluoro*cyclo*butane, the rate constant for the forward reaction, between 300° and 550°, is given by $k = 10{\cdot}3 \times 10^{7}e^{-25,400/RT}$ l. mole^{-1} sec.$^{-1}$ and that for the reverse reaction, between 520° and 590°, by $k = 8{\cdot}9 \times 10^{15}e^{-74,100/RT}$ sec.$^{-1}$. ΔH for the reaction at 527° (800° K) is $-50{\cdot}3$ kcal.

Harmon (U.S.P. 2,404,374) described the major products of the thermal decomposition of tetrafluoroethylene as octafluoro*cyclo*butane and hexafluoro*cyclo*propane; hexafluoropropene was probably wrongly assigned as hexafluoro*cyclo*propane (Young and Murray, *J. Amer. Chem. Soc.*, 1948, **70**, 2814). In the present work quantitative measurements have been made of the rates of the two major reactions concerned in the decomposition. A range of products more extensive than that indicated by Harmon's account has been found.

While this work was in progress, Miller ("Preparation and Technology of Fluorine and Organic Fluorine Compounds," National Nuclear Energy Series, VII—I, 1951, Ch. 32) has reported on the pyrolysis of tetrafluoroethylene in a nickel tube packed with graphite, and Lacher, Tompkin, and Park (*J. Amer. Chem. Soc.*, 1952, **74**, 1693) have determined the activation energy for the dimerisation of tetrafluoroethylene.

Experimental

Apparatus used for Pyrolysis.—(a) *Flow method.* Tetrafluoroethylene from a cylinder was passed through an indicating wash-bottle containing water, a flow meter, a drying tube ($CaCl_2$), and a trap at —12° (the last removed stabilizer). A 60-c.c. cylindrical, silica vessel, internal diameter 21 mm., was used below 600°, and a 180-c.c. steel cylinder, internal diameter 34 mm., above 600°. Each vessel had capillary inlet and outlet tubes, and was heated in a tubular electric furnace, controlled to ±1°. The condensable products were collected in two traps cooled in liquid nitrogen, and the non-condensable material was absorbed on activated charcoal in a trap cooled in liquid nitrogen. A glass-wool filter between the reaction vessel and the traps removed any polymer dust. Pressures on the inflow and outflow sides of each vessel were measured on mercury manometers. A mercury-vapour pump, backed by a rotary oil pump, was used to evacuate the apparatus up to and including the calcium chloride tube.

(b) *Static method.* Two vessels were used. The first was of Pyrex glass, 22 cm. × 4·5 cm. (volume 257·7 ml.), with a capillary inlet 30 cm. long and a coaxial thermocouple-well traversing practically its whole length and extending 22 cm. outside. The second was of steel and of similar but smaller capacity. Its internal surface had to be free from oxide scale, hence it was fabricated of cleaned steel tubing by brazing. It was fitted with a similar thermocouple-well and capillary inlet. Before use the metal vessel was freed from oxide by heating it at 700° and passing a stream of hydrogen through for several hours. A short capillary outlet provided for this purpose was then sealed by welding.

The furnace temperature was controlled by a Sunvic Energy Regulator, by the hand adjustment of which, the temperatures of the reaction vessels were kept within ±0·5°. The chromel–alumel thermocouple was checked against a platinum/platinum–rhodium thermocouple of known reliability.

The vessels were connected by their capillary inlets to a capillary manometer and a two-way tap which led either to a gas reservoir for filling purposes, or to a series of traps for collection of the products. When the dimerization of tetrafluoroethylene was being followed, pressure changes were large and rapid, and readings were to the nearest 0·5 mm. against a scale. In the dissociation of octafluoro*cyclo*butane the pressure changes were small and sufficiently slow to allow them to be measured by cathetometer to the nearest 0·1 mm.

Starting Materials.—(a) *Tetrafluoroethylene.* The gas, from a small cylinder, after passage through the purification system, contained: nitrogen, 1%; hydrogen chloride, 2·5%; and fluorinated ethanes and ethylenes, 3%. It was used in the flow experiments without further purification. For all experiments with the static method, the gas was purified by fractionation in a Podbielniak-type distillation column (Podbielniak, *Ind. Eng. Chem. Anal.*, **1931**, **3**, 177), which was designed to fractionate up to 25 ml. A middle fraction of the tetrafluoroethylene had b. p. −76·5° (Ruff and Bretschneider, *Z. anorg. Chem.*, 1933, **210**, 173, report b. p. −76·3°) (Found: *M*, 99·7, 100·0. Calc. for C_2F_4: *M*, 100·0).

(b) *Octafluorocyclobutane.* The crude tetrafluoroethylene was pyrolysed at 600° and the products were fractionated in the Podbielniak column. The middle portion of the octafluorocyclobutane fraction had b. p. −5·5° (Found: *M*, 200·3. Calc. for C_4F_8: *M*, 200·0), and the infra-red spectrum showed no impurities.

Handling of Products.—(a) *Analysis.* The condensable gases were analysed by fractional distillation in a small Podbielniak type column designed to fractionate up to 5 ml. Yields were determined from the distillation curves in the usual manner.

A Toepler pump was used to transfer gases to a gas burette for measurement or to an Orsat-type of apparatus for analysis. Carbon monoxide was absorbed in acid cuprous chloride solution, and C_2 and C_3 olefins in a 10% solution of potassium bromide saturated with bromine. This reagent absorbed hexafluoropropene satisfactorily, but not C_4 fluoro-olefins. The unsaturation of mixtures of C_4 fluorocarbons was estimated by the semiquantitative potassium permanganate method described by Miller (*op. cit.*).

(b) *Physical properties.* Pure samples for the measurement of physical properties were prepared from the gases separated in the small distillation column either by vacuum fractionation or by redistillation, a middle fraction being taken in the centre of the relevant plateau.

Molecular weights of the condensable products were determined by condensing a known volume into a small bulb and weighing it; for the non-condensable gases the bulb was charged with a little activated charcoal. Vapour pressures were measured by means of an isoteniscope, a copper–constantan thermocouple standardized against an ethylene vapour-pressure thermometer being used for temperature measurement.

TABLE 1

			Products, moles/100 moles of C_2F_4 passed								
Temp.	Vessel	C_2F_4, ml., passed per min.	CF_4	C_2F_4	C_2F_6	C_3F_6	C_4F_8 cyclic	C_4F_8, I *	C_4F_8, II *	Liquids
300°	Silica	19·3	—	94·6	—	—	2·7	—	—	—
400	,,	23·2	—	59·2	—	—	20·4	—	—	—
500	,,	19·4	—	13·5	—	—	43·3	—	—	—
600	,,	18·6	—	2·4	—	5·2	41·7	approx. 0·1 ml. liquid † b. p. > −5·5°		
700	,,	19·0	carbon monoxide and silicon tetrafluoride formed							
400	Steel	59·2	—	59·6	—	—	20·1	—	—	—
600	,,	66·7	—	5·6	—	4·6	39·5	approx. 0·1 ml. liquid † b. p. > −5·5°		
700	,,	60·5	—	—	—	20·5	—	9·4	21·8	2·9
800	,,	62·4	trace	—	25·0	2·1	—	—	16·7	2·5 ‡

* I, b. p. −1° to +4·5°; II, b. p. +6°. † Per litre of tetrafluoroethylene passed.
‡ Also a tar condensed in the exit tube.

The Thermal Decomposition of Tetrafluoroethylene.—(a) *By the flow method.* In each run, about 1 l. of gas (at N.T.P.) was used; and the pressure in the reaction vessel was maintained at 1 atm. Except when the silica vessel was used at 700°, which led to the formation of much carbon monoxide, the non-condensable gases consisted entirely of the nitrogen impurity. The results obtained by fractionation of the condensable material collected are set out in Table 1. A small amount of white polymer dust appeared in the exit tube during runs at 500° and 600°, and carbon was deposited on the walls of the vessel at 800°.

(b) *By the static method.* To ensure that the products formed did not result from the impurities present in the tetrafluoroethylene used in the flow method, the products of a number of runs made by the static method, pure tetrafluoroethylene being used, were collected and fractionated. Runs were carried out at 500° in the silica vessel and at 700° in the steel vessel, and the results showed that the impurities had no appreciable effect on the reactions, except possibly in being the cause of the trace of white polymer mentioned above.

The Properties of the Reaction Products.—The materials isolated by fractionation had the

properties described below. Equations for the vapour-pressure curves are given where these data do not appear in the literature.

(a) *Hexafluoroethane.* M, 137·1 ± 1·0 (Calc. for C_2F_6: M, 138); b. p. −79° ± 1° (from column); m. p. −100·6° ± 1·0° (v. p. curve), in close agreement with the b. p. (−78·3°) and m. p. (−100·7°) recorded by Ruff and Bretschneider (*loc. cit.*).

(b) *Hexafluoropropene.* M, 150·1 ± 0·6 (Calc. for C_3F_6: M, 150); b. p. −30·2° ± 1·0° (v. p. curve); m. p. −155° ± 5° (by observation). Henne and Waalkes (*J. Amer. Chem. Soc.*, 1946, **68**, 496) give b. p. −29·4°, m. p. −156·2°. The vapour pressure between −45° and −95° is given by $\log_{10}p_{mm.} = 7{\cdot}90_8 - 1221/T$ (T in degrees abs.). The gas was slowly absorbed in the bromine reagent, and the permanganate titration showed one double bond per molecule. The infra-red spectrum agreed well with that published by Edgell (*J. Amer. Chem. Soc.*, 1948, **70**, 2816) but gave evidence of the presence of < 1% of octafluoropropane.

(c) *Octafluorocyclobutane.* M, 200·3 ± 0·8 (Calc. for C_4F_8: M, 200); b. p. −5·5° ± 0·5° (v. p. curve); m. p. −38·7° ± 1·0° (v. p. curve). Park, Benning, Downing, Laucius, and McHarness (*Ind. Eng. Chem.*, 1947, **39**, 354) gave b. p. −5°, m. p. −40°. The vapour pressure of the liquid between −38° and −12° is given by $\log_{10}p_{mm.} = 7{\cdot}72_4 - 1295/T$, and for the solid between −50° and −40° by $\log_{10}p_{mm.} = 8{\cdot}93_7 - 1580/T$.

(d) *Octafluorobutenes.* Material from both the flow run at 700° and the static runs at 700° furnished distillation curves with an inflection at −2° followed by a gradual rise in the boiling point until a plateau was reached at 6°.

The material boiling between −2° and +6° from the static run was fractionated into two portions. The middle cut of the first portion, b. p. *ca.* 0°, had M, 202·4 and one double bond. Infra-red spectra indicated that this lower-boiling portion contained not more than a few units % of octafluorobut-1-ene and rather less of some other impurity. We believe it to be a moderately pure sample of an octafluorobutene. The middle cut of the second portion boiled at about 4°, had M 202·6, and was unsaturated to a similar degree. Its infra-red spectrum indicated a mixture of octafluoro-but-1-ene and -but-2-ene. The observed molecular weights suggest that both portions contained some perfluorobutane. The absence of a plateau in the distillation curve shows that the unidentified octafluorobutene present is probably a mixture of *cis*- and *trans*-octafluorobut-2-ene. Henne and Newby (*J. Amer. Chem. Soc.*, 1948, **70**, 130) found that a mixture of these two isomers boiled over the range 0·4° to 3·0°.

The material, b. p. 6°, proved to be identical with that obtained by pyrolysis at 800°; it had M, 200·1 ± 1·0; b. p. 5·7° ± 0·5° (v. p. curve); m. p. −118° ± 5° (by observation). The vapour pressure from −70° to the b. p. is given by $\log_{10}p_{mm} = 8{\cdot}31_6 - 1508/T$. It did not react with the bromine reagent but the permanganate test indicated one double bond. This is undoubtedly the material (b. p. 4·8°) characterized by Miller (*loc. cit.*) as octafluorobut-1-ene, which was his main product at 700°, and the predominant C_4 compound in this temperature region in our experiments. An infra-red spectrum showed the absence of octafluoro*cyclo*butane.

The Rate of Dimerization of Tetrafluoroethylene.—At 300—500° the only product obtained on heating tetrafluoroethylene for a short time was the cyclic dimer. Further investigation showed that this was the only compound formed at 500—550°; thus the rate of dimerization of tetrafluoroethylene over the range 300—550° could be followed by observing the pressure change in a closed system.

Pure tetrafluoroethylene was heated in the " Pyrex " vessel at temperatures between 300° and 550° and at initial pressures between 200 and 550 mm.; pressure–time readings were taken until the reaction was more than half complete. The velocity constants were determined by using formulæ, based on a second-order rate law, which allowed for the influence of dead space. If the reaction

$$2C_2F_4 = <[CF_2]_4> \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

occurs according to the law

$$-d(C_2F_4)/dt = k_1(C_2F_4)^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where (C_2F_4) is expressed in mole l.$^{-1}$, and k_1 in l. mole^{-1} sec.$^{-1}$, and provided there are no other reactions occurring, then

$$k_1t = \frac{760\boldsymbol{R}T_1}{(1-b)[p_0-(p_0-p_t)(1-b)/(\frac{1}{2}-b)]} - \frac{760\boldsymbol{R}T_1}{(1-b)p_0} \quad . \quad . \quad . \quad (3)$$

Pressures are in mm., p_t is the pressure after t secs.; $b = T_1V_2/2(T_2V_1 + T_1V_2)$, where T_1 is the temperature in degrees abs. in the reaction vessel of volume V_1 l., and T_2 the temperature

in the dead space of volume V_2 l. If the second-order rate law is obeyed, the plot of t against $1/[p_0 - (p_0 - p_t)(1 - b)/(\frac{1}{2} - b)]$ should be a straight line of slope $760\boldsymbol{R}T_1/k_1(1 - b)$.

For runs at 450° and below, plots of the above function gave straight lines. At higher temperatures the last few points showed an upward deviation indicating a lower rate of pressure change for the later stages of the reaction than would accord with the presumed law. As no secondary reactions had been detected, it seemed possible that the deviations arose from the reverse reaction as we show below.

$$C_4F_8 = 2C_2F_4 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

In calculating the rate constants, given in Table 2, the initial slopes of the graphs were used where there were deviations from a straight line. The plot of $\log_{10}k_1$ against $1/T$ gave a satisfactory straight line. Rate constants measured at 400°, 425°, and 450° in a vessel packed with small pieces of " Pyrex " glass agreed with those given in Table 2.

The Dissociation of Octafluorocyclobutane.—The pyrolysis of pure octafluoro*cyclo*butane in the " Pyrex " vessel at 550° was accompanied by an increase in pressure; the rate of change decreased with time, suggesting an eventual condition of equilibrium. An adventitious subsequent pressure rise was shown by analysis to be due to the formation of silicon tetrafluoride and carbon monoxide from attack on the glass. There was, however, evidence that in the early stages the attack was small and that the initial slope of the pressure–time curve gave the rate of dissociation of octafluoro*cyclo*butane. To exceed the temperature range and to confirm the above conclusion, it was essential to use a steel vessel, free from oxide scale.

TABLE 2

Temp.	300°	325°	350°	375°	400°	425°	450°	475°	500°	525°	550°
No. of runs	5	5	5	7	6	8	6	5	5	6	6
Mean 10^2k_1, l. mole^{-1} sec.$^{-1}$	2·126	5·410	12·96	28·75	61·39	115·6	219·9	392·1	682·1	1147	1883

In the steel vessel, the pressure increased asymptotically to a virtually constant value after 10 min. at 550°, and after 1½ min. at 590°. This behaviour establishes the simplicity of the system under these conditions, as reactions other than (1) and (4) must be so slow that equilibrium is not measurably disturbed.

For those runs in which the equilibrium pressure was observed, the dissociation rate constant was calculated by three methods, reaction (4) being assumed to be of first order. (i) $\log_{10}(2p_0 - p_t)$ was plotted against t, and since, owing to the occurrence of the reverse reaction, curves are obtained, the initial slopes were taken as corresponding to the rate of the forward reaction only and put equal to $k_2/2{\cdot}303$. (ii) It was assumed that at equilibrium

$$k_2(2p_0 - p_e)/760\boldsymbol{R}T = k_1'[(2p_0 - 2p_e)/760\boldsymbol{R}T]^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

where $k_1' = \frac{1}{2}k_1$, and p_e is the experimentally observed equilibrium pressure. (iii) The following integrated form of the rate equation for approach to equilibrium was used:

$$k_2 = \frac{(p_e - p_0)}{t(3p_0 - p_e)} \cdot 2{\cdot}303 \log_{10} \frac{p_0(p_e - p_0) + (p_t - p_0)(2p_0 - p_e)}{p_0(p_e - p_t)} \quad . \quad . \quad . \quad (6)$$

The plot of the logarithmic term against t is a straight line provided that the assumed orders of reaction are correct; the slope of this line gives k_2.

Only (i) is applicable to the experiments in the " Pyrex " vessel, and the calculated rate constants are given in Table 3. (iii) gave straight-line graphs showing clearly that the dissociation is a first-order reaction. The agreement existing between all the methods at 550° confirms the applicability of (i) to the results in " Pyrex " (see Table 3). The poor concordance at 590° is probably due to the limit being reached in both the experimental method and the applicability of the assumptions implicit in the calculations.

The results obtained by (i) for each temperature were averaged; $\log_{10}k_2$ plotted against $1/T$ gave a straight line.

Activation Energies and other Derived Properties.—For reaction (1) the measurements of the forward rate give the energy of activation, $E = 25{\cdot}4$ kcal. By assuming the molecular diameter, $\sigma = 1{\cdot}33 \times 10^{-8} \sqrt[3]{v}$, where v is the molar volume at the boiling point, and by expressing the rate constant as $k_1 = PZe^{-E/\boldsymbol{R}T}$, where the terms have their usual significance, then the value $P = 3{\cdot}8 \times 10^{-4}$ is obtained. Similarly, for the reverse reaction (4), $E = 74{\cdot}1$ kcal., and in the equation $k_2 = Ae^{-E/\boldsymbol{R}T}$, $A = 8{\cdot}9 \times 10^{15}$ sec^{-1}.

TABLE 3

Temp.	Vessel	Vel. const., 10^5k_2, sec.$^{-1}$, method, (i)	Temp.	Vessel	Vel. const., 10^5k_2, sec.$^{-1}$, method (i)	method (ii)	method (iii)
520°	Pyrex	3·52	550°	Steel	19·80	19·14	17·04
		3·50			18·60	18·72	18·56
		3·52			19·95	19·87	18·70
530	,,	6·44	570	,,	57·57	57·82	56·90
		6·71			59·29	58·41	55·42
		6·42			58·08	57·02	58·03
		6·43			57·05	56·84	56·46
540	,,	10·94	590	,,	142·0	172·8	175·3
		10·37			155·2	138·5	138·1
		10·36			175·0	175·5	176·3
		10·51					
550	,,	18·94					
		19·54					
		19·13					
		19·52					

By use of the standard equations of the transition-state theory of reaction rates (Glasstone, Laidler, and Eyring, "The Theory of Rate Processes," McGraw Hill Book Co., New York, 1941) the following results are obtained (all at 800° abs.):

(i) forward reaction: the entropy of activation at a standard state of one atm. pressure, $\Delta S_p^{\ddagger} = -38{\cdot}4$ cal./degree; the heat of activation, $\Delta H^{\ddagger} = 22{\cdot}2$ kcal.:

(ii) reverse reaction: $\Delta S^{\ddagger} = 10{\cdot}6$ cal./degree; $\Delta H^{\ddagger} = 72{\cdot}6$ kcal. For the complete reaction, ΔE, obtained by subtraction of the E values above, is $-48{\cdot}7$ kcal. From this, $\Delta H = -50{\cdot}3$ kcal. The standard entropy change for a standard state of one atm. pressure, $\Delta S_p^{\circ} = -49{\cdot}2$ cal./degree.

DISCUSSION

There is general agreement between our findings (Table 1) and those of Miller (*loc. cit.*) who used a reaction tube packed with graphite. He found only perfluorobut-1-ene in his butene fraction, however, did not prove the formation of hexafluoroethane, and obtained perfluoropropene at 550°.

At 300—550° there is a simple reversible dimerization of tetrafluoroethylene to octafluoro*cyclo*butane. At 600°, and more so at 700°, perfluoropropene and perfluorobutenes are formed; this requires the transfer of a fluorine from one carbon atom to another, and the high temperature required to allow such reactions to proceed with speed is a demonstration of the high strength of carbon–fluorine bonds.

The mechanism by which perfluoropropene is formed is not known. Perfluorobutenes were always present when the fluoropropene was formed, so the reaction may be

$$C_2F_4 + C_4F_8 = 2C_3F_6 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

This does not account for Miller's observation that the compound was formed at 550° without butenes being formed. In his packed vessel the essential reaction must have been

$$C_2F_4 = 2CF_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

$$\text{or} \quad 2C_2F_4 = C_3F_6 + CF_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

but the reaction may have occurred on the graphite surfaces. It is known that CF_2 free radicals initiate polymerisation of tetrafluoroethylene in the gas phase (Atkinson, *J.*, 1952, 2684). As, at 600° and 700°, we obtained no appreciable amount of solid or tar we doubt whether free radicals are present in the gas phase at these temperatures.

Below 800° the products have the formula $(CF_2)_n$, but at 800° a new mechanism operates since both saturated products of low molecular weight and highly unsaturated products of high molecular weight are formed. The rate of formation of octafluorobutene is undoubtedly fast at this temperature and the observed products are probably derived from the decomposition of this compound to free radicals:

$$CF_3{\cdot}CF_2{\cdot}CF{:}CF_2{\cdot} = CF_3{\cdot} + {\cdot}CF_2{\cdot}CF{:}CF_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

The low yield of tetrafluoromethane shows that abstraction of fluorine, as in equation (12), is slow compared with the union of free radicals to form hexafluoroethane.

$$CF_3\cdot + RF = CF_4 + R\cdot \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

Our values for the rate constant of the dimerization reaction (1) give the equation $k_1 = 10{\cdot}3 \times 10^7 e^{-25{,}400/RT}$ l. mole^{-1} sec.$^{-1}$. Lacher, Tompkin, and Park (*loc. cit.*) found $k_1 = 16{\cdot}5 \times 10^7 e^{-26{,}299/RT}$ l. mole^{-1} sec.$^{-1}$. The P factor for reaction (1) is of the same order as that found by Pease for the dimerization of ethylene to butene (*J. Amer. Chem. Soc.*, 1931, **53**, 613).

The frequency factor for dissociation (4) is high, but this is true for other ring-opening reactions; for *cyclo*propane, $A = 1{\cdot}48 \times 10^{15}$ sec.$^{-1}$ (Chambers and Kistiakowsky, *J. Amer. Chem. Soc.*, 1934, **56**, 399), and for trioxymethylene, $A = 1{\cdot}43 \times 10^{16}$ sec.$^{-1}$ (Burnett and Bell, *Trans. Faraday Soc.*, 1938, **34**, 420). Corresponding with the high frequency factor, the entropy change, despite the loss of one vibrational term theoretically required, is positive and appreciable. The observed value of $\Delta S^{\ddagger}$ may be explained by an open-chain activated state in which there is free rotation about the centre carbon–carbon bond.

No calorimetric data are available for comparison with the kinetically determined heat of dimerization of tetrafluoroethylene, nor have we found in the literature any reliable figures for any similar reaction.

We are grateful to Dr. G. J. Minkoff who determined the infra-red spectra, to the University of London for a grant from the Central Research Fund towards the cost of equipment, to Imperial Chemical Industries Limited, General Chemicals Division, for a gift of tetrafluoroethylene, and to the Department of Scientific and Industrial Research for a maintenance grant which enabled one of us (A. B. T.) to take part in this work.

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425. *The Application of the Arndt–Eistert Reaction to Halogenated Aliphatic Acids.*

By F. Brown and W. K. R. Musgrave.

The Arndt–Eistert reaction has been examined as a means of preparing acids of the series $CX_3\cdot[CH_2]_n\cdot CO_2H$ (where X = Cl or F). Propionic esters were obtained in reasonable yields, but yields of the amide, anilide, and acid were very poor. Since the halogen atoms in βββ-trichloropropionic ester are extremely labile, it appears to be impossible to proceed beyond this member of the chlorinated acid series.

Since trifluoroacetic acid is available commercially it seemed that the easiest way to obtain a series of acids containing the trifluoromethyl group would be by the Arndt–Eistert reaction. This method (for references up to 1942, see Backmann and Struve, "Organic Reactions," John Wiley & Sons, 1942, Vol. I, pp. 38—62) has been applied to halogenated aliphatic acids in only three previous cases (Buckle, Pattison, and Saunders, *J.*, 1949, 1471; Buckle and Saunders, *J.*, 1949, 2774). We now record our attempts to prepare acids of the type $CF_3\cdot[CH_2]_n\cdot CO_2H$ and, for comparison, the trichloro-analogues. Trifluoro- and trichloro-diazoacetone were prepared in yields which, although not as high as those generally obtained from aromatic chlorides, compare very favourably with those usual in the aliphatic series. Both diazo-ketones resemble diazoacetone in being quite stable at room temperature and were distilled under reduced pressure without appreciable decomposition (Wolff, *Annalen*, 1912, **394**, 251; Arndt and Amende, *Ber.*, 1928, **61**, 1122). The yield of trifluorodiazoacetone was particularly dependent on careful distillation and the residue gave two fractions, both containing fluorine and chlorine, which have not been identified because, while residue was being conserved, polymerisation occurred.

Conversion of the diazo-ketones into the esters of the homologous acids was much

more successful than into the amides and the yield of chlorinated ester was much superior to that of the fluorinated ester. Direct preparations of the higher anilide and free acid were attempted only from trifluorodiazoacetone; because yields from this were poor and because the chlorine atoms in derivatives of trichloropropionic acid were so labile that treatment even with very weak alkali caused hydrolysis, the work was not extended to trichlorodiazoacetone.

Acid hydrolysis of trichloropropionic ester also failed to give the free acid (cf. Ladd and Sargent, U.S.P. 2,515,306, for hydrolysis of γγγ-trichlorobutyric esters) and it was concluded that further ascent of this series was not practicable. In the trifluoro-acids further ascent would be tedious but, despite this, the method is simpler and gives yields as good as other available processes (Henne, Pelley, and Alm, *J. Amer. Chem. Soc.*, **1950**, **72**, 3370; McBee and Truchan, *ibid.*, 1948, **70**, 2910).

Experimental

Trifluorodiazoacetone.—Trifluoroacetyl chloride (11·7 g., 0·09 g. mol.) (Henne, Alm, and Smook, *J. Amer. Chem. Soc.*, 1948, **70**, 1968) was slowly distilled (at least 1 hr.) into stirred, ice-cold, ethereal diazomethane (0·22 mole in 600 ml.). There was vigorous evolution of nitrogen which ceased as soon as all of the acid chloride had been added. After at least 2 hr. the mixture was allowed to reach room temperature, and the ether was distilled at 35° (bath-temperature) through an 8″ column packed with Fenske helices in a very slow stream of air. Vacuum-distillation of the residue gave *trifluorodiazoacetone* (7·5 g., 62·5%), b. p. 25°/1 mm. (Found: F, 41·2. $C_3HON_2F_3$ requires F, 41·3%).

Ethyl βββ-*Trifluoropropionate.*—Trifluorodiazoacetone (7 g.) in absolute alcohol (150 ml.) was stirred at 65° and a slurry of silver oxide [from 20% silver nitrate (20 ml.)] in absolute alcohol (40 ml.) added at intervals during 30 min., nitrogen being evolved and some of the silver oxide reduced. The mixture was then refluxed for 18 hr., treated with charcoal, cooled, and filtered, and the solvent distilled off through a column. Distillation of the residue gave *ethyl* βββ-*trifluoropropionate* (3·1 g., 40·4%), b. p. 50°/12 mm., n_D^{24} 1·3912 (Found: F, 36·4%; equiv., 159, 152. $C_5H_7O_2F_3$ requires F, 36·5%; equiv., 156).

Trichlorodiazoacetone.—This was prepared similarly from trichloroacetyl chloride (15 g., 0·08 mole) in ether (100 ml.) and diazomethane (0·21 mole) in ether (600 ml.). Evolution of nitrogen continued for about 1 hr. after the addition of the chloride and the mixture was kept overnight at room temperature before the ether was removed under reduced pressure at 20°. Vacuum-distillation of the residue gave *trichlorodiazoacetone* (13·6 g., 88%), b. p. 60°/1 mm. (Found: Cl, 56·7. $C_3HON_2Cl_3$ requires Cl, 56·5%).

Ethyl βββ-*Trichloropropionate.*—The ester was prepared in the same way as the trifluoro-derivative from trichlorodiazoacetone (13·6 g.) in absolute alcohol (200 ml.) and the same amount of silver oxide slurry. After 29 hr.' refluxing distillation of the residue left after removal of the alcohol gave *ethyl* βββ-*trichloropropionate* (11 g., 74%), b. p. 97°/14 mm., n_D^{20} 1·5140 (Found: Cl, 51·8. $C_5H_7O_2Cl_3$ requires Cl, 51·8%). Equivalent-weight determinations with 0·5N-sodium hydroxide at 100° gave values of 55, 56, and 53 owing to hydrolysis of all three chlorine atoms.

Malonamide from βββ-*Trichloropropionic Ester.*—Ethyl trichloropropionate (5 g.) was refluxed at 110° for 3 hr. with an excess of aqueous sodium hydroxide (7·8 g. in 300 ml.), and the resultant homogeneous solution neutralised with N-hydrochloric acid (the volume of acid required indicated 93% hydrolysis). After evaporation to dryness the sodium salts were refluxed for 4 hr. with absolute alcohol (200 ml.) containing concentrated sulphuric acid (3 ml.). After cooling, neutralisation with sodium ethoxide, and centrifuging, the alcohol was distilled off. The residue of malonic ester (0·8 g.), b. p. 93°/17 mm., gave, after distillation and treatment with liquid ammonia, malonamide (0·09 g.), m. p. and mixed m. p. 170° (from water).

βββ-*Trifluoropropionamide.*—Trifluorodiazoacetone (5·5 g.) in absolute alcohol (150 ml.) was treated with a slurry of silver oxide (from 20 ml. of 20% silver nitrate solution), cooled in ice-water, and stirred while dry ammonia was bubbled in for 1¼ hr., then allowed to attain room temperature (2—4 hr.). Ammonia was passed for a further 1½ hr. before heating with charcoal under reflux until excess of ammonia was expelled. Filtration and distillation of the solvent left a solid which on distillation gave βββ-*trifluoropropionamide* (0·7 g.), b. p. 130°/12 mm. The liquid crystallised to a deliquescent white solid at room temperature. Warming (50°) with 1—2 c.c. of 0·1N-hydrochloric acid, followed by evaporation to dryness, gave the

ammonium salt (0·7 g., 12·4%), purified by sublimation at 136°/21 mm. (Found: F, 39·1; N, 9·7. Calc. for $C_3H_6O_2F_3N$: F, 39·3; N, 9·6%).

Attempts to prepare the amide in dioxan with aqueous ammonia (Arndt and Eistert, *Ber.*, 1935, **68**, 200; Berger and Avakian, *J. Org. Chem.*, 1940, **5**, 606) and to isolate the product as ammonium salt were unsuccessful.

The ammonium salt was also prepared from the ester (1 g.) by treatment with ammonium chloride (2 crystals) and liquid ammonia (excess). Evaporation of the ammonia left colourless crystals of the ammonium salt (0·5 g., 61·5%) which could not be distilled but sublimed (136°/20 mm.) (Found: N, 9·7%).

ββγ-*Trichloropropionamide.*—Trichlorodiazoacetone (9·3 g.) in absolute alcohol (200 ml.) was treated as was the trifluoro-compound. After distillation of the solvent the brown solid residue was purified by sublimation (150°/8 mm.), to give ββγ-*trichloropropionamide* (0·46 g., 5·3%) (Found: Cl, 60·1; N, 7·9. $C_3H_4ONCl_3$ requires Cl, 60·3; N, 7·9%).

ββγ-*Trifluoropropionanilide.*—The method is based on that of Arndt and Eistert (*loc. cit.*), trifluorodiazoacetone (7·7 g.) being added gradually to a well-stirred solution of aniline (15 ml.) and 10% aqueous silver nitrate (20 ml.) in dioxan (150 ml.) at room temperature. The temperature was then raised to 115° during 2 hr. and kept thereat for 15 hr. The hot mixture was filtered, treated with charcoal, and evaporated to one-third volume. Crude product (1·5 g.) separated. Recrystallisation from alcohol gave pure ββγ-trifluoropropionanilide (1·0 g., 8·9%), m. p. 118° (Found: F, 27·9. Calc. for $C_9H_8ONF_3$: F, 28·1%). Henne, Pelley, and Alm (*loc. cit.*) give m. p. 117·5—118°.

ββγ-*Trifluoropropionic Acid.*—This was prepared by Walker's method (*J.*, 1940, 1304) from trifluorodiazoacetone (6·1 g.) in warm dioxan (166 ml.), fresh silver oxide (11·7 g.), and aqueous sodium thiosulphate (18·4 g. in 420 ml.). After 1·5 hr.' heating at 75° the mixture was allowed to cool and kept overnight. A small amount (*ca.* 0·1 g.) of ββγ-trifluoropropionic acid, b. p. 144° (Found: F, 44·6. Calc. for $C_3H_3O_2F_3$: F, 44·5%) was obtained. Henne and Fox (*J. Amer. Chem. Soc.*, 1951, **73**, 2323) give f. p. 9·7°, b. p. 144·8°.

The sodium salt was prepared from the ethyl ester and the ammonium salt by hydrolysis with 0·1N-sodium hydroxide. From this were prepared the S-*benzylthiuronium*, m. p. 176° (from alcohol) (Found: F, 19·6. $C_{11}H_{13}O_2N_2SF_3$ requires F, 19·4%) (for method see Wild, "Organic Compounds," Cambridge Univ. Press, 1947, p. 148), and the *aniline* salt, m. p. 116° (from alcohol) (Found: equiv., 223. $C_9H_{10}O_2F_3N$ requires equiv., 221) by mixing dry ethereal solutions of the acid and aniline.

S-*Benzylthiuronium trifluoroacetate*, m. p. 173° (Found: F, 20·6. $C_{10}H_{11}O_2N_2SF_3$ requires F, 20·4%), and *aniline trifluoroacetate*, m. p. 122° (Found: F, 27·4%; equiv., 211. $C_8H_8O_2NF_3$ requires F, 27·54%; equiv., 207), were also prepared by the same method.

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The University, South Road, Durham. [*Received, February 26th*, 1953.]

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426. *Synthesis of Plant-growth Regulators. Part II.* Dichloro-β-naphthyloxyacetic Acids.*

By (Miss) P. M. James and D. Woodcock.

1 : 6-Dichloro-2-naphthol (previously recorded m. p. 119·5°) has been synthesised by three routes and shown to have m. p. 99—100°. A mode of formation of 1 : *x*-dichloro-2-naphthols is described and new dichloro-2-naphthyloxyacetic acids, prepared as potential parthenocarpic or systemic fungicidal agents, are reported. Hydriodic acid, which demethylates chloromethoxynaphthalenes, causes elimination of α-chlorine atoms. Whilst hydrobromic acid demethylates normally in some cases, it converts 1 : 8-dichloro- into 8-bromo-1-chloro-2-naphthol.

The preparation of 1 : 6-dichloro-2-naphthol, claimed by Ruggli, Knapp, Merz, and Zimmermann (*Helv. Chim. Acta*, 1929, **12**, 1051), has already been discussed (James and

* Part I, *J.*, 1951, 3418.

Woodcock, *J.*, 1951, 1931). This naphthol was first mentioned in D.R.-P. 431,165 where reduction to 6-chloro-2-naphthol by ferrous sulphate is described, but there was no mention of the origin of the dichloro-compound or of its melting point.

Initial attempts were made to obtain 1 : 6-dichloro-2-naphthol from 1 : 6-disubstituted 2-naphthol or 2-naphthylamine derivatives. 1 : 6-Dichloro-2-naphthylamine, by diazotisation and hydrolysis, gave only a dark red alkali-insoluble material; the Sandmeyer reaction conditions, however, produced 1 : 2 : 6-trichloronaphthalene in high yield. Tetrazotisation of 1 : 6-diamino-2-naphthol or its methyl ether, followed by hydrolysis, gave only tars. Finally, the desired naphthol was produced in minute yield by the route : 6 : 2-$C_{10}H_8Cl{\cdot}OH$ ⟶ 6 : 1 : 2-$C_{10}H_7Cl(NO_2){\cdot}OH$ ⟶ 6 : 1 : 2-$C_{10}H_7Cl(NH_2){\cdot}OH$ ⟶ 6 : 1 : 2-$C_{10}H_7Cl_2{\cdot}OH$. It was later obtained from 6-chloro-2-naphthol by treatment with sodium hypochlorite under certain conditions, and this method proved to be general for the formation of dichloro- from the remaining monochloro-2-naphthols. Entry of the second chlorine atom at position 1 was confirmed by the isolation of the known 1 : 3- and 1 : 4-dichloro-2-naphthols from the 3- and 4-chloro-2-naphthols respectively.

Nitration of 1-chloro-2-methoxynaphthalene gave two easily separable mononitro-derivatives, reduction of which, followed by diazotisation and Sandmeyer reactions, led to 1 : 6- and 1 : 8-dichloro-2-methoxynaphthalene. Attempts to demethylate these compounds led to similar treatment of other mono- and di-chloro-2-methoxynaphthalenes. Hydriodic acid eliminated chlorine from the α- but not from the β-position (cf. Franzen and Stäuble, *J. pr. Chem.*, 1921, **103**, 382), whilst hydrobromic acid generally only attacked the ether linkage. Hydrobromic–acetic acid converted 1 : 6-dichloro-2-methoxynaphthalene into 1 : 6-dichloro-2-naphthol, but with the 1 : 8-dichloro-ether yielded 8-bromo-1-chloro-2-naphthol. The identity of this compound was confirmed by synthesis from 8-chloro-7-methoxy-1-naphthylamine.

Whilst we were unable to produce 1-chloro-6-nitro-2-naphthol from the corresponding amine by diazotisation and subsequent hydrolysis, a Sandmeyer reaction gave 1 : 2-dichloro-6-nitronaphthalene in good yield. Reduction, diazotisation, and hydrolysis then gave the new 5 : 6-dichloro-2-naphthol.

Direct chlorination of 6-chloro-2-naphthol gave an alkali-insoluble product, probably a tetrachlorodihydroketonaphthalene, which on reduction with zinc dust was converted into, presumably, 1 : 3 : 6- or 1 : 4 : 6-trichloro-2-naphthol since oxidation with alkaline potassium permanganate yielded 4-chlorophthalic acid. Reduction with hydriodic acid gave a di- and not a mono-chloro-2-naphthol, however, showing that the trichloro-compound was 1 : 3 : 6-trichloro-2-naphthol. The reduction product, 3 : 6-dichloro-2-naphthol, may have been prepared by Claus and Schmidt (*Ber.*, 1886, **19**, 3172) and by Pollak (*Monatsh.*, 1929, **49**, 187) but in neither case was the orientation confirmed. In our hands, the former workers' method failed to give any phenolic material.

The results of the tests of both naphthols and naphthyloxyacetic acid as parthenocarpic and systemic fungicidal agents will be submitted for publication elsewhere.

Experimental

6-Chloro-2-naphthol.—The following procedure was more convenient and gave a better yield than that reported in Part I. 6-Nitro-2-naphthylamine (Saunders and Hamilton, *J. Amer. Chem. Soc.*, 1932, **54**, 638), diazotised in hydrochloric acid solution, gave, by a Sandmeyer reaction, 2-chloro-6-nitronaphthalene which, recrystallised once from dioxan, had m. p. 170—172°. Reduction in tetrahydrofuran in presence of Raney nickel gave 6-chloro-2-naphthylamine, m. p. 121—123°. The diazotised amine was hydrolysed by pouring it into boiling 20% sulphuric acid and a red product obtained. 6-Chloro-2-naphthol obtained by extraction of this product with 5% aqueous sodium hydroxide had m. p. 117—118° (yield based on nitro-amine, 37%). *6-Chloro-1-(6-chloro-2-naphthylazo)-2-naphthol* crystallised from dioxan in red needles, m. p. 234—236° (Found : C, 65·5; H, 3·4; Cl, 18·8. $C_{20}H_{12}ON_2Cl_2$ requires C, 65·4; H, 3·3; Cl, 19·3%). The m. p. was undepressed on admixture with the product obtained by coupling diazotised 6-chloro-2-naphthylamine and 6-chloro-2-naphthol.

6-Chloro-1-nitro-2-naphthol.—6-Chloro-2-naphthol (2 g.) in acetic acid (20 ml.) was added

slowly dropwise to a cooled mixture of fuming nitric acid (4 ml.) and acetic acid (15 ml.). After a further 1 hr.'s stirring at 0—5°, the mixture was poured on ice, and the product collected, washed with water and dried (1·6 g.; m. p. 129—131°). 6-*Chloro*-1-*nitro*-2-*naphthol* crystallised from aqueous methyl alcohol in dark yellow, rectangular prisms, m. p. 136—137° (Found: C, 53·7; H, 2·5; Cl, 15·8. $C_{10}H_6O_3NCl$ requires C, 53·7; H, 2·7; Cl, 15·9%). The *acetate* crystallised from acetic acid in colourless monoclinic prisms, m. p. 130—131° (Found: C, 54·2; H, 3·0; Cl, 13·0. $C_{12}H_8O_4NCl$ requires C, 54·2; H, 3·0; Cl, 13·4%). The *methyl ether*, which could only be prepared by refluxing the dry, finely powdered sodium salt of the naphthol with methyl sulphate, crystallised from dioxan in pale green rectangular prisms, m. p. 153—154° (Found: C, 55·8; H, 3·5; Cl, 14·4. $C_{11}H_8O_3NCl$ requires C, 55·6; H, 3·4; Cl, 14·9%).

1-*Amino*-6-*chloro*-2-*naphthol*.—6-Chloro-1-nitro-2-naphthol (3 g.) in tetrahydrofuran (20 ml.) was shaken in hydrogen in the presence of Raney nickel until no further gas was absorbed. Removal of the solvent from the filtered solution and crystallisation of the residue from aqueous methyl alcohol gave the *amino-naphthol* as colourless rhombs (2·2 g.), m. p. 177—178° (Found: C, 62·1; H, 4·3; Cl, 18·3. $C_{10}H_8ONCl$ requires C, 62·0; H, 4·1; Cl, 18·3%). The *diacetyl* derivative crystallised from aqueous methyl alcohol in rhombic prisms, m. p. 144—145° (Found: C, 60·8; H, 4·5; Cl, 13·0. $C_{14}H_{12}O_3NCl$ requires C, 60·5; H, 4·3; Cl, 12·8%).

1 : 6-*Dichloro*-2-*naphthol*.—(*a*) The above amino-naphthol (1·5 g.) was dissolved in glacial acetic acid (15 ml.) and concentrated sulphuric acid (4 ml.) and cooled to 0°. Sodium nitrite (0·5 g.) was added and stirring continued for 2 hr. The mixture was then added to cuprous chloride (5 g.) in concentrated hydrochloric acid (25 ml.) and stirred at room temperature for 15 min. The product, isolated with ether and re-extraction of the ethereal solution with alkali, was a dark solid. Further extraction with boiling light petroleum (b. p. 60—80°) gave rectangular prisms, m. p. 89—93°, raised to 97—99° by recrystallisation from the same solvent. This compound did not depress the m. p. of 1 : 6-dichloro-2-naphthol prepared as described below.

(*b*) 1 : 6-Dichloro-2-naphthylamine (Clemo and Legg, *J.*, 1947, 539) (1 g.) in concentrated hydrochloric acid (3 ml.) and water (10 ml.) was diazotised at 0° with sodium nitrite (0·5 g.). Addition of the filtered diazonium solution to boiling 20% sulphuric acid (300 ml.) caused no immediate effervescence but after several mintues the precipitation of a red solid was observed; no alkali-soluble material was isolated. When Sandmeyer conditions were used, the product was 1 : 2 : 6-trichloronaphthalene (0·9 g.), m. p. 91—92°, undepressed by admixture with an authentic specimen.

1 : 2-*Dichloro*-6-*nitronaphthalene*.—1-Chloro-6-nitro-2-naphthylamine (Clemo and Legg, *loc. cit.*) (5 g.), diazotised as already described, was added to a solution of cuprous chloride (5 g.) in concentrated hydrochloric acid (50 ml.), and the mixture warmed on a water-bath until the evolution of nitrogen had ceased. The *product*, washed with water and dried at 100° (5·1 g.), crystallised from aqueous dioxan in orange rectangular prisms, m. p. 170—171° (Found: C, 49·8; H, 2·1. $C_{10}H_5O_2NCl_2$ requires C, 49·6; H, 2·1%).

5 : 6-*Dichloro*-2-*naphthylamine*.—The preceding product (3·2 g.) in tetrahydrofuran (30 ml.) was shaken with Raney nickel until no further hydrogen was absorbed. The *amine*, on removal of the solvent from the filtered solution, crystallised from aqueous methyl alcohol in light brown, monoclinic prisms, m. p. 123—124° (Found: C, 56·8; H, 3·5; Cl, 33·1. $C_{10}H_7NCl_2$ requires C, 56·6; H, 3·3; Cl, 33·5%).

5 : 6-*Dichloro*-2-*naphthol*.—Diazotisation of 5 : 6-dichloro-2-naphthylamine and hydrolysis of the diazonium solution as described for 6-chloro-2-naphthol, gave 5 : 6-dichloro-2-naphthol (cf. below) in 40% yield.

Nitration of 1-*Chloro*-2-*methoxynaphthalene*.—A mixture of fuming nitric acid (*d* 1·5; 24 ml.) and acetic acid (120 ml.) was stirred at 5—10° for 45 min. during the addition of the methyl ether (15·5 g.) in acetic acid (120 ml.). Stirring was continued for a further 2·5 hr. at room temperature and then water (100 ml.) was added. The crystalline precipitate (A) which had gradually increased in amount was collected and washed with water. Further addition of water to the mother-liquors gave a second crop (B) which was treated similarly.

1-*Chloro*-2-*methoxy*-6-*nitronaphthalene* [product (A)] crystallised from acetone–ethyl alcohol in monoclinic prisms, m. p. 181—182° (Found: C, 55·4; H, 3·4; Cl, 14·6. $C_{11}H_8O_3NCl$ requires C, 55·6; H, 3·4; Cl, 14·9%). 1-*Chloro*-2-*methoxy*-8-*nitronaphthalene* [product (B)] crystallised from aqueous ethyl alcohol in rhombic prisms, m. p. 106—108° (Found: C, 55·6; H, 3·3; Cl, 15·2%).

5-*Chloro*-6-*methoxy*-2-*naphthylamine*.—This was obtained by shaking the appropriate nitro-compound in tetrahydrofuran in the presence of Raney nickel and hydrogen. When reduction

was complete, the catalyst was filtered off and the solvent removed. The *amine* crystallised from methyl alcohol in colourless stout rhombs, m. p. 117—118° (Found: C, 63·7; H, 5·0; Cl, 16·5. $C_{11}H_{10}ONCl$ requires C, 63·6; H, 4·8; Cl, 17·1%).

8-*Chloro*-7-*methoxy*-1-*naphthylamine*.—Prepared as was the isomer, this *amine* crystallised from methyl alcohol in colourless monoclinic prisms, m. p. 91—92° (Found: C, 63·6; H, 4·8; Cl, 17·0%).

1 : 6-*Dichloro*-2-*methoxynaphthalene*.—A solution of 5-chloro-6-methoxy-2-naphthylamine (1·6 g.) in water (10 ml.) and concentrated hydrochloric acid (10 ml.) was treated at 0° with sodium nitrite (0·7 g.). After 0·25 hr. the filtered solution was added to a solution of cuprous chloride (1·7 g.) in concentrated hydrochloric acid (20 ml.) and stirred at room temperature until the evolution of nitrogen ceased. The *dichloro*-compound, washed with water and dried, crystallised from light petroleum (b. p. 40—60°) (charcoal) in colourless monoclinic prisms, m. p. 70—71° (Found: C, 58·2; H, 3·7; Cl, 31·2. $C_{11}H_8OCl_2$ requires C, 58·1; H, 3·5; Cl, 31·2%). Admixture with the product obtained by methylating 1 : 6-dichloro-2-naphthol failed to depress the m. p. Oxidation in pyridine with potassium permanganate gave 4-chlorophthalic acid, m. p. 150° undepressed by admixture with an authentic specimen. Demethylation by refluxing hydriodic acid (*d* 1·7) and a trace of red phosphorus (4 hr.) gave 6-chloro-2-naphthol, m. p. and mixed m. p. 115—117°. Similar treatment in acetic acid with hydrobromic acid (*d* 1·7) gave 1 : 6-dichloro-2-naphthol, m. p. 98—99°, identical with the products previously described.

1 : 8-*Dichloro*-2-*methoxynaphthalene*.—Prepared as was the isomer, this *compound* crystallised from light petroleum (b. p. 40—60°) in rectangular prisms, m. p. 71—72° (Found: C, 58·1; H, 3·6; Cl, 30·8%). Admixture with the product obtained by methylating 1 : 8-dichloro-2-naphthol (described below) failed to depress the m. p. Oxidation with powdered potassium permanganate in pyridine gave 3-chlorophthalic acid, m. p. 179—181°, whilst demethylation with hydriodic acid (*d* 1·7) yielded β-naphthol, m. p. 120—121°, each undepressed by admixture with the appropriate authentic specimen.

8-*Bromo*-1-*chloro*-2-*methoxynaphthalene*.—A solution of 8-chloro-7-methoxy-1-naphthylamine (1·5 g.), diazotised in 33% sulphuric acid, was poured into a solution of cuprous bromide (1·5 g.) in hydrobromic acid (*d* 1·5; 15 ml.) and kept at ordinary temperature for 1 hr. Extraction with ether gave a red tar from which the *bromo*-compound was obtained by extraction with light petroleum (b. p. 60—80°). It crystallised from light petroleum (b. p. 40°) in rectangular prisms, m. p. 58—59° (Found: C, 48·5; H, 3·0. $C_{11}H_8OBrCl$ requires C, 48·6; H, 2·9%).

8-*Bromo*-1-*chloro*-2-*naphthol*.—(*a*) A solution of 1 : 8-dichloro-2-methoxynaphthalene (1·0 g.) in acetic acid (10 ml.) was refluxed with hydrobromic acid (*d* 1·7; 5 ml.) for 4 hr. The *product*, isolated with ether, crystallised from acetic acid in colourless rectangular prisms, m. p. 144—145° (Found: C, 46·4; H, 2·5; Br, 30·6; Cl, 13·6. $C_{10}H_6OBrCl$ requires C, 46·4; H, 2·3; Br, 31·0; Cl, 13·8%).

(*b*) Treatment of 8-bromo-1-chloro-2-methoxynaphthalene by the same procedure gave a product, m. p. 140—142°, which did not depress the m. p. of product (*a*). The *acetate* prepared from product (*a*) or (*b*) crystallised from aqueous methyl alcohol in rectangular prisms, m. p. 97—98° (Found: C, 48·0; H, 2·6. $C_{12}H_8O_2BrCl$ requires C, 48·1; H, 2·7%).

1 : 3-*Dichloro*-2-*methoxynaphthalene*.—This *compound* crystallised from aqueous methyl alcohol in prisms, m. p. 49—50° (Found: C, 58·0; H, 3·7; Cl, 31·4. $C_{11}H_8OCl_2$ requires C, 58·1; H, 3·5; Cl, 31·2%). Demethylation with (*a*) hydriodic acid (*d* 1·7) and (*b*) hydrobromic acid (*d* 1·7) in acetic acid, gave 3-chloro-2-naphthol, m. p. 92—93°, and 1 : 3-dichloro-2-naphthol, m. p. 71—73°, respectively. The identities of these products were confirmed by admixture with authentic specimens.

1 : 4-*Dichloro*-2-*methoxynaphthalene*.—This *compound* crystallised from ethyl alcohol in rectangular prisms, m. p. 84—85° (Found: C, 58·1; H, 3·5; Cl, 31·2. $C_{11}H_8OCl_2$ requires C, 58·1; H, 3·5; Cl, 31·2%). Demethylation with hydriodic acid (*d* 1·7) gave β-naphthol, m. p. and mixed m. p. 120—121°. Hydrobromic acid (*d* 1·7) in acetic acid gave 1 : 4-dichloro-2-naphthol, m. p. and mixed m. p. 121—122°.

1-*Chloro*-6-*nitro*-2-*naphthol*.—A solution of 1-chloro-2-naphthol (1·0 g.) in glacial acetic acid (10 ml.) was added dropwise during 0·25 hr. to a mixture of nitric acid (*d* 1·5) (2 ml.) and acetic acid (10 ml.) and stirred at room temperature for 1 hr. further. Water (*ca.* 10 ml.) was added and the crystalline precipitate which gradually formed was collected, washed with water, and dried (0·2 g.; m. p. 170—186°). The *nitronaphthol* crystallised from aqueous methyl alcohol in yellow rectangular prisms, m. p. 194—195° (Found: C, 53·5; H, 2·6; Cl, 15·7. $C_{10}H_6O_3NCl$ requires C, 53·7; H, 2·7; Cl, 15·9%). This result was only reproduced once; many other

attempts gave tars. The methyl ether had m. p. 180—181°, undepressed by admixture with 1-chloro-2-methoxy-6-nitronaphthalene described earlier.

2-*Acetoxy*-1 : 6-*dinitronaphthalene*.—The *acetyl* derivative prepared from 1 : 6-dinitro-2-naphthol (Bell, *J.*, 1930, 1932) crystallised from benzene (charcoal) in nacreous plates, m. p. 172—173° (Found : C, 52·1; H, 2·6. $C_{12}H_8O_6N_2$ requires C, 52·2; H, 2·8%).

Chlorination of 6-*Chloro*-2-*naphthol*.—The naphthol (0·5 g.) in tetrahydrofuran (5 ml.) was subjected to a slow stream of dry chlorine at 0°. After removal of the solvent the *substance* produced crystallised from methyl alcohol in brownish monoclinic prisms, m. p. 157—159° (Found : C, 42·6; H, 1·4; Cl, 49·8. $C_{10}H_4OCl_4$ requires C, 42·6; H, 1·4; Cl, 50·3%).

1 : 3 : 6-*Trichloro*-2-*naphthol*.—A solution of the preceding tetrachloro-product (1 g.) in glacial acetic acid (20 ml.) was refluxed with zinc dust (2 g.) for 1 hr. Addition of water to the hot filtered solution gave 1 : 3 : 6-trichloro-2-naphthol which crystallised from aqueous acetic acid in colourless needles, m. p. 98—99° (Found : C, 48·3; H, 2·0. $C_{10}H_5OCl_3$ requires C, 48·5; H, 2·0%). The *acetate* crystallised from aqueous methyl alcohol in colourless monoclinic prisms, m. p. 109—110° (Found : C, 49·8; H, 2·5. $C_{12}H_7O_2Cl_3$ requires C, 49·8; H, 2·4%).

3 : 6-*Dichloro*-2-*naphthol*.—Treatment of the above trichloronaphthol with boiling hydriodic acid (*d* 1·7) for 4 hr. gave an alkali-soluble *product* which crystallised from light petroleum (b. p. 60—80°) in colourless rectangular prisms, m. p. 124—125°. The *acetate* crystallised from aqueous methyl alcohol in nacreous plates, m. p. 98—99°. For analyses see the Table.

Chloro-substituents	M. p.	Solvent *	Found (%) : C	H	Chloro-substituents	M. p	Solvent *	Found (%) : C	H
	Dichloro-2-naphthols.[1]					*Dichloro-2-naphthyl acetates.*[2]			
1 : 5-	143—144°	Aq. AcOH	56·5	2·9	1 : 5-	100—101°	MeOH	56·4	3·3
1 : 6-	99—100	Pet. (40—60°)	56·1	2·9	1 : 6-	98—99	Aq. AcOH	56·7	3·1
1 : 7-	121—122	Aq. AcOH	55·9	2·7	1 : 7-	111—112	Aq. MeOH	56·4	3·1
1 : 8-	126—127	Aq. MeOH	56·5	2·8	1 : 8-	87—88	,,	56·4	3·1
3 : 6-	124—125	Pet. (60—80°)	56·3	2·9	3 : 6-	98—99	,,	56·5	3·0
5 : 6-	151—152	,,	56·4	3·0	5 : 6-	92—93	,,	56·5	3·0
	Dichloro-2-naphthyloxyacetic acids.[3]								
1 : 5-	206—207°	MeOH	53·0	3·2					
1 : 6-	162—163	Aq. MeOH	53·4	3·0					
1 : 7-	176—177	,,	53·2	3·0					
1 : 8-	156—157	,,	53·15	3·2					
3 : 6-	179—180	,,	53·2	3·0					
5 : 6-	192—193	,,	53·4	2·8					

* Pet. = light petroleum (b. p. in parentheses).
[1] $C_{10}H_6OCl_2$ requires C, 56·35; H, 2·8%.
[2] $C_{12}H_8O_2Cl_2$ requires C, 56·5; H, 3·1%.
[3] $C_{12}H_8O_3Cl_2$ requires C, 53·15; H, 3·0%.

1 : x-*Dichloro*-2-*naphthols*.—The appropriate monochloronaphthol, dissolved in aqueous sodium hydroxide (1 equiv.), was stirred at 0—5° during the dropwise addition of aqueous sodium hypochlorite (4% w/v of available chlorine, 1 equiv.). Use of more concentrated hypochlorite solution gave tars but more dilute solutions have been successfully used. After 0·5 hr. the solution was acidified and the product collected, washed with water, dried, and recrystallised. For the products see the Table.

Dichloro-2-*naphthyloxyacetic acids*.—These were prepared as described in Part I; analytical details are tabulated.

The authors thank Mr. R. F. Batt and Mr. J. F. Harris for the halogen analyses.

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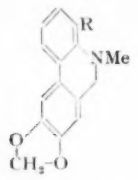
427. *A Synthesis of* 1-*Ethyl*-9 : 10-*dihydro*-10-*methyl*-6 : 7-*methylenedioxyphenanthridine.*

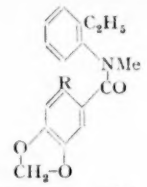
By R. B. Kelly, W. I. Taylor, and K. Wiesner.

A synthesis of 1-ethyl-9 : 10-dihydro-10-methyl-6 : 7-methylenedioxyphenanthridine is described, the properties of which are in agreement with those reported for dihydrolycorine anhydromethine. The structure of lycorine is discussed.

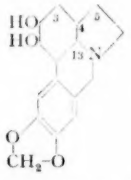
Kondo and his co-workers have based their structural formula for lycorine (Kondo and Katsura, *Ber.*, 1940, **73**, 1424; and earlier papers) on the structure which they assigned to its Hofmann degradation product, lycorine anhydromethine (I). Neither (I) nor its hydrogenation product dihydrolycorine anhydromethine (II) has been synthesized, but the formula (I) was deduced from the products of its oxidation (Kondo and Uyeo, *Ber.*, 1935, **68**, 1756) and from the isolation of 1-ethyl-6 : 7-methylenedioxyphenanthridine on zinc dust distillation of dihydrolycorine anhydromethine (*idem*, *Ber.*, 1937, **70**, 1087). Since rearrangement of the nucleus may have attended the zinc dust distillation it seemed to us that a logical approach to a new discussion of the constitution of lycorine should be an unambiguous synthesis of either (I) or (II).



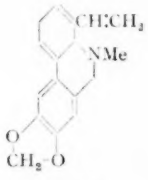
(I; R = $CH{:}CH_2$)
(II; R = C_2H_5)



(III; R = NO_2)
(IV; R = NH_2)



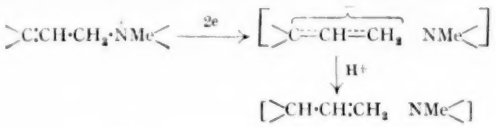
(V; 4 : 13-double bond)
(VI; 4 : 5- „ „)



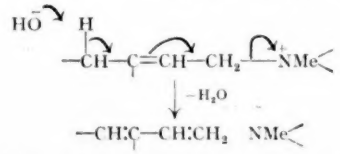
(VII)

Reduction of *o*-ethylformanilide with lithium aluminium hydride afforded *o*-ethyl-*N*-methylaniline which was condensed with 4 : 5-methylenedioxy-2-nitrobenzoyl chloride to yield *o'*-ethyl-*N*-methyl-4 : 5-methylenedioxy-2-nitrobenzanilide (III). Hydrogenation of (III) over Raney nickel gave 2-amino-*o'*-ethyl-*N*-methyl-4 : 5-methylenedioxybenzanilide (IV) which was subjected to the Pschorr reaction; the crude 1-ethyl-10-methyl-6 : 7-methylenedioxyphenanthridone formed was reduced with lithium aluminium hydride to 1-ethyl-9 : 10-dihydro-10-methyl-6 : 7-methylenedioxyphenanthridine (II). The melting points of synthetic (II) and its picrate were identical with those reported for dihydrolycorine anhydromethine (*idem*, *ibid.*).

Scheme *A*



Scheme *B*



If in the Hofmann degradation of lycorine methohydroxide to the anhydromethine base (I) no rearrangement has occurred, then lycorine must possess the tetracyclic system present in the structure (V) which Kondo and Katsura (*loc. cit.*) have suggested for the alkaloid. Emde reduction of lycorine methochloride, like the Hofmann degradation, proceeds with the loss of the vicinal hydroxyl groups and affords, not, as might have been

expected on the basis of (V) for lycorine, dihydrolycorine anhydromethine (II), but an isomer *which contains a vinyl group*. If, however, the double bond is in the 4 : 5-position (as VI), then the Emde reduction would proceed initially by the attack of two electrons followed by addition of a proton to the mesomeric anion with the resultant allylic shift to produce a vinyl group and a tertiary amine (scheme *A*).

The final Emde product is probably (VII) for which the ultra-violet absorption spectrum ($\lambda_{max.}$ 297 mμ, log ε 3·86; Kondo and Katsura, *loc. cit.*) is in good agreement. The Hofmann degradation is pictured as starting by elimination of a proton from the carbon atom δ to the quaternary nitrogen atom (scheme *B*), followed by elimination of two molecules of water to give lycorine anhydromethine (I). Further work to substantiate the proposed formula (VI) for lycorine is in progress.

Added in Proof.—Through the kindness of Dr. S. Uyeo, Osaka, Japan, we have shown that our synthetic 1-ethyl-9 : 10-dihydro-10-methyl-6 : 7-methylenedioxyphenanthridine is identical with authentic dihydrolycorine anhydromethine in melting point, mixed melting point, and infra-red spectrum.

Experimental

o-*Ethylformanilide*.—*o*-Ethylaniline (35 g.) and formic acid (13·2 g.) were heated on a water-bath for 30 min., after which the temperature was raised slowly to 240° to allow water and excess of formic acid to distill off. After cooling, ether (50 c.c.) was added to the mixture and pure o-*ethylformanilide* (28 g.), m. p. 70°, crystallized. For analysis it was recrystallized from ether and dried *in vacuo* at room temperature for 48 hr. (Found : C, 72·4; H, 7·4; N, 9·0. $C_9H_{11}ON$ requires C, 72·5; H, 7·4; N, 9·4%).

o-*Ethyl*-N-*methylaniline*.—*o*-Ethylformanilide (25 g.) in ether (500 c.c.) was added dropwise to ether (1 l.) containing lithium aluminium hydride (10 g.) and then heated for 15 hr. under reflux. Water was carefully added and after the vigorous reaction had subsided the ethereal solution was separated and the aqueous residue extracted three times with ether. The combined ethereal extracts were dried (Na_2SO_4) and concentrated to dryness, to yield the crude base which after distillation afforded pure o-*ethyl*-N-*methylaniline* (21·8 g.), b. p. 95—97°/11 mm. It gave a *picrate*, m. p. 136—138°, from methanol (Found, in a sample dried *in vacuo* at 45° for 48 hr. : C, 49·6; H, 4·4; N, 15·3. $C_{15}H_{16}O_7N_4$ requires C, 49·5; H, 4·4; N, 15·4%).

o'-Ethyl-N-*methyl*-4 : 5-*methylenedioxy*-2-*nitrobenzanilide* (III).—4 : 5-Methylenedioxy-2-nitrobenzoyl chloride (from 10 g. of acid) was added slowly to a stirred solution of *o*-ethyl-*N*-methylaniline (7 g.) and pyridine (15 c.c.) in ether (500 c.c.). After 48 hr. the mixture was washed with 5% potassium carbonate solution (500 c.c.), then twice with water. The aqueous washings were extracted with ether, and the combined dried ethereal extracts were concentrated to dryness *in vacuo* to give a viscous brown oil (14·4 g.) which was taken up in chloroform and filtered through activated alumina 500 g.). Concentration of the chloroform eluate afforded the crude crystalline o-*ethyl*-N-*methyl*-4 : 5-*methylenedioxy*-2-*nitrobenzanilide* (14 g.), m. p. 106° constant after one crystallization from ether (Found, in a sample dried *in vacuo* at 65° for 48 hr.: C, 62·1; H, 5·0; N, 8·5. $C_{17}H_{16}O_5N_2$ requires C, 62·2; H, 4·9; N, 8·5%).

2-*Amino*-o'-*ethyl*-N-*methyl*-4 : 5-*methylenedioxybenzanilide* (IV).—An ethanolic solution of the preceding anilide (10 g.) took up the theoretical volume of hydrogen in 1 hr. in the presence of Raney nickel. The solution was filtered, concentrated to dryness, to yield after one crystallization from ether pure 2-*amino*-o'-*ethyl*-N-*methyl*-4 : 5-*methylenedioxybenzanilide* (8·5 g.), m. p. 121° (Found, in a sample dried *in vacuo* at 60° for 48 hr.: C, 68·5; H, 6·1; N, 9·5. $C_{17}H_{18}O_3N_2$ requires C, 68·4; H, 6·1; N, 9·4%).

1-*Ethyl*-9 : 10-*dihydro*-10-*methyl*-6 : 7-*methylenedioxyphenanthridine* (II).—Sodium nitrite (0·8 g. in 5 c.c. of water) was added to an ice-cold solution of 2-amino-o'-ethyl-*N*-methyl-4 : 5-methylenedioxybenzanilide (2·8 g.) in 5% sulphuric acid (100 c.c.). After 1 hr. the pale yellow solution was heated slowly to 75° and kept thereat for 2 hr. during the slow nitrogen evolution and finally at 100° for 30 min. The mixture was extracted five times with chloroform which was then washed with 10% aqueous sodium hydroxide and water. Evaporation of the dried (Na_2SO_4) chloroform extract gave a dark brown tar (840 mg.) which was chromatographed in ether over activated alumina (2·5 g.). The ether eluate (1300 c.c.) yielded on concentration a pale yellow wax which after sublimation (130—150°/0·1 mm.) yielded crude 1-*ethyl*-10-*methyl*-6 : 7-*methylenedioxyphenanthridone* (255 mg., 10%). The whole of the crude phenanthridone was refluxed for 15 hr. in ether with lithium aluminium hydride (1 g.). Addition of water and extraction with ether afforded a yellow oil (205 mg.) which was converted into a crystalline

picrate (142 mg.), m. p. 175° (decomp.) (from methanol). For analysis the *1-ethyl-9 : 10-dihydro-10-methyl-6 : 7-methylenedioxyphenanthridine picrate* was dried *in vacuo* at 80° for 48 hr. (Found: C, 55·5; H, 4·2; N, 11·1. $C_{23}H_{20}O_9N_4$ requires C, 55·6; H, 4·1; N, 11·1%).

A chloroform solution of the picrate was filtered through a short column of activated alumina, then concentrated to dryness, to give the base (22 mg.), m. p. 87° constant after one crystallization from ether–light petroleum (b. p. 30—60°) (Found, in a sublimed sample: C, 76·1; H, 6·2. $C_{17}H_{17}O_2N$ requires C, 76·4; H, 6·4%).

We are indebted to the National Research Council, Canada, for a grant and a N.R.C. fellowship to one of us (R. B. K.), and to the Monsanto Chemicals Limited, St. Louis, for a gift of *o*-ethylnitrobenzene which was used for the preparation of *o*-ethylaniline.

THE CHEMICAL LABORATORIES,
THE UNIVERSITY OF NEW BRUNSWICK. [*Received, April 1st, 1953.*]

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428. *Determinations of Electrokinetic Charge and Potential by the Sedimentation Method. Part IV.* Silica in Conductivity Water.*

By D. P. BENTON and G. A. H. ELTON.

The sedimentation-velocity method for the determination of electrokinetic charge and potential is applied to the study of fused silica surfaces in conductivity water of various qualities. Contrary to reports by some previous workers, a systematic trend is found in the value of these quantities with the conductivity of the water.

DETERMINATIONS of the electrokinetic charge and potential at the silica–potassium chloride solution, silica–sodium chloride solution, and silica–hydrochloric acid solution interfaces (Parts I and III *) have shown that, at corresponding concentrations in the range 5×10^{-5}N —2×10^{-5}N, although the charges and potentials in potassium chloride and sodium chloride solutions are closely similar, yet those in the acid are considerably lower. This difference in the charge is about 250 e.s.u. at 5×10^{-5}N and increases to about 750 e.s.u. at 2×10^{-3}N. At concentrations below 2×10^{-5}N, the charge and potential become very similar at all three interfaces.

The solutions used in these experiments were made up in "equilibrium water," *i.e.*, conductivity water which had been allowed to come into equilibrium with the atmosphere. The conductivity of this water was of the order 1 gemmho, depending on atmospheric conditions, and may be attributed (see, *e.g.*, Davies, "Conductivity of Solutions," Chapman and Hall, London, 1933) to hydrogen and bicarbonate ions provided by dissociation of carbonic acid formed from dissolved carbon dioxide.

The concentration (2—5×10^{-5}N) at which the difference ($\Delta\sigma$) between the charge in the salt solutions from that in the acid solution becomes appreciable is approximately the concentration at which ionisation of dissolved carbonic acid becomes negligible in acid solutions. It might, therefore, be suggested that a charge exists at the silica–water interface due to adsorption of bicarbonate ions (and/or OH′, CO_3''), this charge persisting when a neutral salt is added to the system but being stripped off by a sufficient concentration of acid. In a salt solution the charge due to bicarbonate ion (and/or OH′, CO_3'') will depend on the magnitude of the affinity of these ions for the surface (adsorption potential) and the repulsion owing to the negative electrical potential at the surface. As this electrical potential is made less negative by increased salt concentration, the repulsion will be reduced, and it is to be expected that the contribution to the charge of the bicarbonate ion (and/or OH′, CO_3'') will be larger. This may account in part for the increased value of $\Delta\sigma$ as the concentration is increased. Furthermore, although a solution, 2×10^{-5}N with respect to acid, may contain a sufficiently small number of bicarbonate, hydroxyl, and carbonate ions to render their contribution to the conductivity negligible, these ions may still make an appreciable contribution to the charge if they possess large adsorption potentials. Hence,

* Parts I, II, and III, *J.*, 1952, 286, 2953; 1953, 1168.

from the point of view of the surface, a concentration of acid greater than 2×10^{-5}N may be needed to render the effect of bicarbonate, hydroxyl, and carbonate ions completely negligible.

The experimental work described here was carried out in order to investigate the charge and potential at the silica–water interface and any systematic variation of these quantities with the carbonic acid content of the water. The sedimentation velocities of a particle-sized specimen of fused silica powder were measured in water of various qualities, *i.e.*, carbon dioxide content. The electrokinetic charges, σ, at the interface were calculated by the expression

$$\sigma^2 = \frac{g\kappa(u_0 - u)(\rho_2 - \rho_1)}{MA_0^2 u u_0 \rho_2}$$

where g = gravitational constant, κ = specific conductivity (e.s.u.) of the suspension, u_0 and u = rate of settling of the suspension in concentrated electrolyte solutions, *i.e.*, in absence of electroviscosity and in a given solution respectively; ρ_2, ρ_1 = densities of silica and solution respectively; M = mass of particles per ml. of suspension; A_0 = area per g. of particles.

The results given in the Tables and the Figures show that the velocity of sedimentation is close to the limiting velocity in water of high purity and decreases markedly as the water becomes equilibrated with the atmosphere. The charge is seen to rise from 125 e.s.u. in the purest water obtained to somewhat over 500 e.s.u. in water of conductivity 1 gemmho.

FIG. 1.

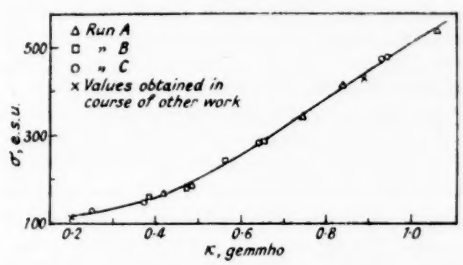
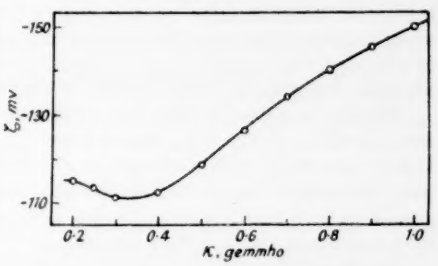


FIG. 2.



κ, gemmho	u, cm./sec. $\times 10^3$	Charge σ, e.s.u.	κ, gemmho	u, cm./sec. $\times 10^3$	Charge σ, e.s.u.	κ, gemmho	u, cm./sec. $\times 10^3$	Charge σ, e.s.u.
Runs A and *B*: Mass of silica per ml. of suspension = $8{\cdot}096 \times 10^{-4}$ g., area per g. of silica = $1{\cdot}20 \times 10^4$ sq. cm., limiting velocity = $3{\cdot}497 \times 10^{-3}$ cm./sec.								
0·3843	3·337	157·6	0·5616	3·245	241·2	0·8345	3·000	409·0
0·4173	3·317	165·5	0·6497	3·187	284·6	0·9358	2·924	471·1
0·4709	3·333	167·4	0·7240	3·100	339·0	1·056	2·863	532·0
Run C: Mass of silica per ml. of suspension = $5{\cdot}740 \times 10^{-4}$ g., area per g. of silica = $1{\cdot}40 \times 10^4$ sq. cm., limiting velocity = $3{\cdot}033 \times 10^{-3}$ cm./sec.								
0·2495	2·905	126·0	0·4836	2·896	181·8	0·9240	2·604	469·0
0·3696	2·916	146·4	0·6376	2·795	280·1			

κ, gemmho	σ, e.s.u.	$n_H = n_{HCO_3} + n_{OH}$, ions/ml. $\times 10^{-14}$	ζ, mv	κ, gemmho	σ, e.s.u.	$n_H = n_{HCO_3} + n_{OH}$, ions/ml. $\times 10^{-14}$	ζ, mv
0·2	115	3·011	−115·2	0·6	255	9·111	−127·5
0·25	125	3·778	−113·7	0·7	317	10·64	−134·7
0·3	130	4·544	−111·0	0·8	380	12·16	−140·5
0·4	156	6·072	−112·9	0·9	444	13·69	−145·4
0·5	197	7·598	−119·0	1·0	510	15·21	−150·0

The charge-determining ion at the silica–water interface is probably the bicarbonate ion, although in any calculation of the electrokinetic potential we must consider the possible contribution due to hydroxyl and carbonate ions. The calculation using Verwey and Overbeek's expression ("Theory of the Stability of Lyophobic Colloids," 1948, Elsevier Publ. Co. Inc., London), *viz.*,

$$\sigma = \left[\frac{2n\varepsilon kT}{\pi}\right]^{\frac{1}{2}} \sinh \frac{ze\zeta}{2kT}$$

(where n = number of charge-determining ions of valency z per ml., ε = dielectric constant in the electrical double layer, k = Boltzmann's constant, e = electronic charge, T = absolute temperature, ζ = electrokinetic potential) may not be strictly correct, since it was derived for a single electrolyte species. For a system containing a number of ions of mixed valencies the appropriate corresponding expression is

$$\sigma = \left[\frac{\varepsilon kT}{2\pi}\right]^{\frac{1}{2}} [\Sigma n_i (e^{-z_i e\zeta/kT} - 1)]^{\frac{1}{2}}$$

where n_i is the number of ions, species i, of valency z_i, per ml.

The numbers of ions, n_{H}, n_{HCO_3}, n_{OH}, n_{CO_3} in conductivity water may be calculated from the measured conductivity, the dissociation constants of carbonic acid, and the ionic product of water, if the conductivity is assumed to be due to these ions (Davies, *op. cit.*). Calculation on these lines shows that the contribution of the carbonate ion to the summation term in the above expression is negligible. The expression then reduces to Verwey and Overbeek's expression with $n = n_{H} = n_{OH} + n_{HCO_3}$.

The electrokinetic potentials at the silica–water interface have therefore been calculated by using Verwey and Overbeek's expression and are shown plotted against the conductivity of the water in Fig. 2. The values of the charge, σ, used in these calculations were taken from the smoothed σ–κ graph shown in Fig. 1.

It is noteworthy that these results indicate that the electrokinetic potential increases with increasing concentration of bicarbonate ion. This is contrary to the usual behaviour observed in aqueous electrolyte solutions, where the electrokinetic potential decreases with increasing concentration of the charge-determining ion. The usual tendency towards lower values of the potential at higher concentrations owing to the decrease in the thickness of the electrical double layer is outweighed in this case by the unusually rapid rate of increase of charge, due presumably to the operation of a high adsorption potential.

Wood (*J. Amer. Chem. Soc.*, 1946, **68**, 437) carried out many streaming-potential measurements at the silica–water interface. He found no systematic trend in the electrokinetic potentials with conductivity of the water and gave a value of −177 mv as the mean over the whole range of conductivity in which he worked. However, the variation of his results at ony one conductivity was often greater than the total variation in our figures over the whole range 0·2—1 gemmho.

Lachs and Biczyk (*Z. physikal. Chem.*, 1930, *A*, **148**, 441), using the streaming-potential method, report electrokinetic potentials at the silica–water interface as a function of the specific conductivity of the water ranging from −146 mv for water of conductivity 0·72 gemmho to −55 mv for water of conductivity 3 gemmho. The trend in the electrokinetic potential is in the reverse direction to that shown in our results, but it is doubtful if the impurities in the water used by Lachs and Biczyk were entirely carbonic acid, since conductivity water in equilibrium with a normal atmosphere rarely possesses a conductivity far in excess of 1 gemmho. Their results are, therefore, not comparable with the present measurements except perhaps in the case of their purest water (0·72 gemmho), where the difference is only a few mv.

Finally, we may conclude, from the agreement obtained between runs *A* and *B* (with water from a conventional still) on the one hand, and run *C* on the other, that water purified by the ion-exchange method is apparently free from undesirable surface-active impurities.

Experimental

Materials.—Particle-sized specimens of fused silica powder were kindly provided by Mr. C. I. Dulin. Specimens were cleaned by boiling aqua regia and washed many times with conductivity water, the washings being removed after centrifugation. Later stages of washings were carried out with water of conductivity 0·25—0·4 gemmho.

Conductivity water was obtained for runs *A* and *B* from a still of the type described by Bourdillon (*J.*, 1913, **103**, 791) and modified by Bengough, Stuart, and Lee (*J.*, 1927, 2156). For run *C* the water was obtained by passing good distilled water through a column packed with resin, Biodemineralite, supplied by the Permutit Co.

Sedimentation Experiments.—These were carried out in a cylindrical cell, of 4-cm. diameter,

graduated with a vertical scale in mm. Electrodes sealed into the bottom of the cell enabled the conductivity of the suspension to be determined by using an A.C. bridge. The cell was fitted with a ground-glass stopper at the top, which had, in turn, two subsidiary ground-glass stoppered inlets.

The silica specimen was washed into the cell, then allowed to settle, and the supernatant water poured off. A stream of nitrogen was then blown through the cell *via* a tube passing through one of the subsidiary inlets and reaching to the bottom of the cell. The tube was then removed, and the cell fitted directly to the tin receiver of the still (runs *A* and *B*) or to the delivery tube of the ion-exchange column (run *C*). The cell, thus filled with the purest conductivity water available, was clamped vertically in a thermostat at 25° ± 0·01°. The sedimentation velocity and the conductivity of the suspension were measured. A subsidiary stopper at the top of the cell was then removed for a short time, and the cell gently shaken. This contact of the water in the cell with the atmosphere caused the conductivity to increase. The sedimentation velocity and the conductivity were again measured. The procedure was repeated several times; each time the sedimentation velocity and the conductivity were measured.

The limiting velocity, u_0 was determined after adding concentrated hydrochloric acid to make an approximately N-solution. The mass of particles per ml. was determined by weighing the particles separated from a known volume of suspension. The density of the silica was determined in a density bottle, and the area per g. of the particles determined by the method of catalytic decomposition of hydrogen peroxide (Part I, *loc. cit.*).

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BATTERSEA POLYTECHNIC, S.W.11. [*Received, December 9th*, 1952.]

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429. *Determination of Electrokinetic Charge and Potential by the Sedimentation Method. Part V.* Silica in Some Aqueous Nitrate Solutions.*

By C. I. DULIN and G. A. H. ELTON.

Electrokinetic charges and potentials of fused silica surfaces in dilute aqueous solutions of various nitrates are determined by the sedimentation method. For univalent cations, the results for nitrates are close to those for the corresponding chlorides, confirming that the adsorption energies of the nitrate and chloride ions are similar, but for higher-valency cations there is an increasing tendency towards higher charges in the nitrate solutions. Possible causes of this effect are discussed.

THIS paper gives the results of measurements by the sedimentation method of the electrokinetic charges and potentials of fused silica surfaces in dilute aqueous solutions of potassium, barium, lanthanum, and thorium nitrates, and of nitric acid. Results for the corresponding chloride solutions were reported in Parts I and III (Dulin and Elton, *J.*, 1952, 286; 1953, 1168). The Table gives the values of the charge, σ, calculated as described previously from the measured sedimentation velocities of homodisperse suspensions of fused silica powder in the nitrate solutions. In the case of lanthanum and thorium nitrates, increase of concentration from zero brings about reversal of the initial negative charge, owing to ready adsorption of the high-valency cation (and hydrolysis products) into the fixed part of the double layer. In the region of the isoelectric point, the values given in the Table are of lower accuracy than usual, since the measured sedimentation velocity, u, is very near to the limiting velocity, u_0, and fairly small errors in the determination of either of these velocities result in relatively large errors in the values of $(u_0 - u)$, required in the calculation of σ. Calculation of ζ, the potential across the diffuse part of the double layer, from σ is straightforward for uni-univalent electrolytes, but is more complicated for solutions containing high-valency ions, especially when hydrolysis is considerable, as, *e.g.*, with thorium nitrate solutions. The hydrolysis

* Part IV, preceding paper.

correction in the calculation of ζ, for the case of cation hydrolysis, is more important when the charge is negative, *i.e.*, when the hydrolysed ion is acting as a counter-ion (see Dulin and Elton, 1953, *loc. cit.*). For thorium nitrate, this occurs only below 2×10^{-5}N, but for lanthanum nitrate the charge is negative at all concentrations below 5×10^{-4}N, and hydrolysis corrections have to be applied as described previously. Although, for

	σ, e.s.u./cm.²					ζ, mv				
c, N	HNO_3	KNO_3	$Ba(NO_3)_2$	$La(NO_3)_3$	$Th(NO_3)_4$	HNO_3	KNO_3	$Ba(NO_3)_2$	$La(NO_3)_3$	$Th(NO_3)_4$
1×10^{-3}	3770	4207	1369	1718 *	4928 *	99·5	105·0	34·5	66·1 *	114·0 *
5×10^{-4}	3107	3391	1413	0	2883 *	107·2	112·4	43·1	0	104·9 *
2×10^{-4}	2228	2491	1355	496	1368 *	113·5	118·4	53·2	23·6	91·4 *
1×10^{-4}	1772	1991	1201	643	744 *	119·4	125·3	58·8	32·4	80·3 *
5×10^{-5}	1418	1570	1001	633	368 *	125·7	130·9	63·0	36·0	60·4 *
2×10^{-5}	1013	1187	856	532	0	132·0	140·0	70·7	44·4	0
1×10^{-5}	822	1017	750	487	160	138·5	149·8	76·1	49·3	23·3
5×10^{-6}	—	—	713	484	202	—	—	83·7	55·2	30·8
2×10^{-6}	—	—	678	452	370	—	—	94·2	59·0	43·8
1×10^{-6}	—	—	691	—	527	—	—	103·8	—	53·0

All values are negative except those marked *.

convenient reference, both charges and potentials are given in the Table, the results are discussed below solely in terms of the charges, in view of the uncertainties inherent in the calculation of the potentials.

Discussion.—The charge in nitric acid solutions is always lower than in potassium nitrate solutions of the same concentration, the difference being about 200 e.s.u. at 1×10^{-5}N, rising steadily to about 700 e.s.u. at 2×10^{-3}N. Similar differences were found between the results for hydrochloric acid and potassium chloride, and were ascribed to the stripping off in acid solutions of the charge due to ions from the solvent. The charges in nitric acid are close to those in hydrochloric acid, the differences over most of the range being less than 5%. There is a slight trend in the differences, the charge for nitric acid being rather lower in the most dilute solutions, and higher in the more concentrated solutions. The similarity between the two sets of results indicates that the energy of adsorption of the nitrate ion on to a fused silica surface cannot differ greatly from that of the chloride ion. This deduction has been confirmed by Benton and Elton (*Trans. Faraday Soc.*, 1953, in the press), quantitative experiments giving values of −2·48 kcal. for the nitrate ion, and −2·44 kcal. for the chloride ion, for adsorption from 10^{-4}N-solutions. The results for potassium nitrate are almost identical with those for potassium chloride at 10^{-3}N, but show a slight but definite trend towards lower relative values as the concentration decreases, a parallel trend to that mentioned above for nitric acid.

Barium nitrate differs appreciably from barium chloride, the charges over the range 10^{-6}—10^{-4}N being about 100 e.s.u. higher. Over the range 10^{-4}—10^{-3}N the difference rises to almost 500 e.s.u. The accuracy in the latter range is rather low, errors of the order of 100 e.s.u. being possible owing to low values of $(u_0 - u)$. Although the adsorption energies of the nitrate and chloride ions have been shown to be nearly the same, a higher negative charge may be obtained for the nitrate solutions for the following reason. It is known that in solutions of nitrates of bivalent cations, the tendency to form ion-pairs is much greater than in solutions of the corresponding chlorides (see, *e.g.*, Robinson, *ibid.*, 1940, **36**, 735, 1135; Robinson and Stokes, *ibid.*, p. 1137). Since a singly charged ion-pair will be less strongly attracted to the negatively charged surface than a doubly charged cation, a larger negative charge will be obtained, provided that the ion-pair does not possess an abnormally high adsorption energy.

A rather similar effect may occur in lanthanum nitrate solutions. In the most dilute solutions, a negative charge almost equal to that in lanthanum chloride solutions is obtained, but at concentrations just below the isoelectric point, 5×10^{-4}N, the nitrate charge is rather more negative than the chloride charge. On the positive side of the isoelectric point the nitrate charge is more positive than the chloride charge, possibly owing to the low electrostatic repulsion by the surface of ion-pairs from the nitrate solution. In this case, however, hydrolysis is a complicating factor.

Thorium nitrate is strongly hydrolysed, and the large number of ionic species in the solutions renders analysis of the results difficult, since each species possesses its own characteristic adsorption energy. The charge in the most dilute nitrate solutions is considerably more negative than in the corresponding chloride solutions, the isoelectric point being 2×10^{-5}N, compared with 4×10^{-6}N. On the positive side of the isoelectric point, the nitrate charge increases rapidly, and has become more positive than the chloride charge by 10^{-3}N, indicating strong adsorption of a positively charged species from the nitrate solutions.

BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, March 5th*, 1953.]

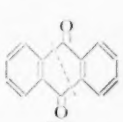
430. *Spectra of Anthraquinone Derivatives.*

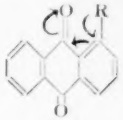
By R. H. PETERS and H. H. SUMNER.

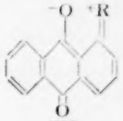
The absorption spectra of a number of mono- and di-substituted anthraquinones have been measured, and the effect of the substituents on the visible colour of anthraquinone has been correlated with the electromeric possibilities of the groups. The wave-length of maximum absorption also depends on the ability of the substituents to take part in internal hydrogen bonds and on the presence of steric interactions in the molecule. Interaction between 1 : 4-substituents is demonstrated, the position of the absorption peak of 1-amino-4-R-anthraquinone depending on the nature of R. This effect is much less marked in the 1 : 5-compounds. Results showing the effect of chromophoric insulation in a series of derivatives containing two anthraquinone nuclei are included. It is found that methylene groups, and both *m*- and *p*-phenylene residues act as excellent chromophoric insulators in the compounds studied.

THE relation between the colour and the constitution of anthraquinone derivatives has been studied by Morton and Earlam (*J.*, 1941, 159) and by Spruit (*Rec. Trav. chim.*, 1949, **68**, 325) for both the visible and the ultra-violet region of the spectrum. They concluded that for simple substituted anthraquinones the spectra may be obtained by summation from less complex series. For instance, Morton and Earlam constructed the spectrum of anthraquinone from twice that of acetophenone plus a contribution from a chromophore of the type (I), the weak visible band originating in the carbonyl groups of the latter. The spectrum was therefore regarded as arising from the two halves of the molecule divided diagonally as in (II). Spruit, on the other hand, derived the spectra of simple anthraquinone derivatives from the algebraic sum of those of the substituted naphthaquinones corresponding to the two halves of the molecules; *e.g.*, anthraquinone gave a spectrum which is double that of 1 : 4-naphthaquinone. He thus attributed the weak visible band to a " fundamental " electronic oscillation of naphthaquinone, and not of anthraquinone. This suggests that the visible spectrum of an anthraquinone derivative arises from a particular part of the molecule and, as such, the visible bands would be described in the terminology of G. N. Lewis as " partials " (Lewis and Calvin, *Chem. Reviews*, 1939, **25**, 273). However, it is to be expected that strongly coloured substituted anthraquinones will

(I)


(II)


(III)


(IV)

show bands due to the molecule as a whole, *i.e.*, " fundamentals : " indeed, the intensity of the yellow colour of benzoquinone, naphthaquinone, and anthraquinone decreases in that order, which may be associated with the decreasing quinonoid character of the molecules, as suggested by Morton and Earlam (*loc. cit.*).

In benzoquinone the molecule is mainly quinonoid, whilst in naphthaquinone the second ring has two Kekulé structures; the additional resonance will change the double-bond character of the bond common to both rings, thereby reducing the quinonoid character of the molecule. In anthraquinone, with two benzene rings capable of resonance, this effect is even more marked; and the visible band of this compound is very weak.

A substituent in these nuclei will affect the resonance, causing either a change in the existing bands associated with the quinonoid part of the molecule, or development of new absorption bands arising from new resonance possibilities. The groups normally regarded as auxochromes may be expected to act in the latter way. Change in the existing bands has been studied in detail by Morton and Earlam (*loc. cit.*); the work now reported is concerned in the main with the new bands. We append some observations on the spectra of anthraquinone compounds which show strong absorption bands in the visible region of the spectrum. These bands are attributed to " fundamental " oscillations in the molecule, and their positions are correlated with the electromeric properties of the substituents.

Mono-substituted Anthraquinones.—The above views are similar to those given by Spruit (*loc. cit.*) and Allen, Wilson, and Frame (*J. Org. Chem.*, **1942**, **7**, 169), who have postulated that the visible colour of substituted anthraquinones depends on the ability of the substituents to supply electrons by a " mesomeric shift " to the nucleus, and in particular to the carbonyl oxygen of the quinonoid grouping, as indicated in (III), thereby increasing the contribution from (IV). Such ionic states are considered to be the optically important resonance forms, and hence the substitution of any group which has an atom more capable of carrying a positive charge than the carbon atom of the unsubstituted molecule will lower the energy of these forms and increase their contribution to the system. Enhancement of these forms will give an increase in colour, which will be generally shown as a shift in absorption to longer wave-length or by development of a new band. However, before considering the visible colour of these compounds it is necessary to discuss the ultra-violet absorption.

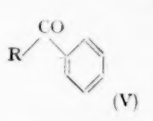
The ultra-violet absorption spectrum of anthraquinone can be considered to originate

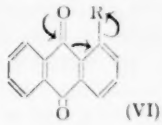
TABLE 1. *Ultra-violet absorption peaks of monosubstituted anthraquinones in methanolic solution.*

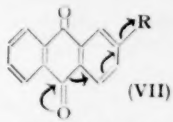
Substituent R	1-R-Anthraquinone				2-R-Anthraquinone			
	" Benzenoid " bands *		" Quinonoid " bands *		" Benzenoid " bands *		" Quinonoid " bands *	
NO_2	255 (37,000)	325 (4,300)	—	—	258 (39,700)	323 (5,200)	—	—
CN	257 (43,000)	325 (3,400)	—	~272 (ca. 12,000	255 (48,600)	325 (5,300)	—	~270 (ca. 18,000)
Cl	253 (42,800)	333 (5,000)	~266 (ca. 14,000)	~270 (ca. 13,000)	256 (49,400)	325 (3,900)	~265 (ca. 23,000)	274 (17,100)
H	252 (48,100)	323 (4,500)	~262 (ca. 20,000)	272 (18,400)	252 (48,100)	323 (4,500)	~262 (ca. 20,000)	272 (18,400)
Me	252 (45,200)	331 (4,800)	~263 (ca. 18,000)	272 (14,500)	—	—	—	—
OH	252 (29,000)	327 (3,300)	~266 (ca. 14,000)	~277 (ca. 12,000)	245 (20,500)	328 (4,400)	271 (33,600)	~279 (ca. 28,000)
OMe	254 (32,800)	328 (2,900)	~262 (ca. 23,000)	~270 (ca. 15,000)	246 (16,200)	329 (3,600)	267 (32,700)	~280 (ca. 24,000)
NH_2	236 (32,200)	298 (5,500)	261 (12,400)	~270 (ca. 11,000)	242 (31,300)	~327 (ca. 9,000)	~286 (ca. 21,000)	298 (23,500)
O^-	246 (35,000)	313 (5,000)	—	273 (11,400)	243 (31,900)	~338 (ca. 7,000)	~285 (ca. 17,000)	304 (23,100)
NHMe	243 (31,400)	312 (7,000)	—	272 (11,000)	243 (31,200)	~345 (ca. 8,000)	~287 (ca. 17,000)	303 (21,400)
NMe_2	246 (33,000)	317 (6,400)	—	~272 (ca. 11,000)	244 (31,800)	352 (8,900)	~290 (ca. 15,000)	307 (19,600)

~ denotes inflexion. * Wave-length, mμ (extinction coefficient).

in contributions from the chromophoric systems, (I) and (V) (Morton and Earlam, *loc. cit.*). The bands at 252 and 325 mμ are associated with the benzenoid character of the molecule, and those at 263 and 272 mμ are considered to originate in the C:C bond of the quinone (I). These bands are still evident, more or less modified, in substituted anthraquinones. Electron-attracting substituents do not much alter the absorption spectrum (see Table 1), owing mainly to the counteracting influence of the carbonyl oxygen which hinders transfer of electrons across the molecule as in (VI) and (VII). The most noticeable effect in the


(V)


(VI)


(VII)

1-position is the decrease in intensity of absorption, while for the 2-derivatives even this effect is absent, the changes occurring being merely small alterations in the position of the maxima.

Electron-donating substituents have more marked effects on the ultra-violet absorption spectra. For the 1-derivatives the band at 252 mμ shows in general a lower intensity and a trend towards shorter wave-lengths as one proceeds downwards from H in Table 1, while for the band at 325 mμ the changes are more random, being bathochromic with reduced intensity for Me, OH, and OMe, and hypsochromic with increased intensity for NH_2, O^-, NHMe, and NMe_2. For these derivatives there is little change in those bands associated with the quinonoid structure, except that again there appears to be a tendency for the intensity to be diminished by substitution. For the 2-derivatives a hypsochromic shift of the band at 252 mμ, and bathochromic shifts of the bands at 323, 262, and 272 mμ are observed. Associated with these changes is an increase in intensity of the band at 272 mμ, due to contributions of structures of type (VIII). This is particularly noticeable for 2-hydroxyanthraquinone where the bands at 271 and 279 are notably more intense. These results for electron-donating substituents accord with the observations of Morton and Earlam (*loc. cit.*) who suggest that substitution at position 1 decreases the importance of the quinonoid element, while substitution at position 2 increases it.

TABLE 2. *Visible absorption bands of monosubstituted anthraquinones.*

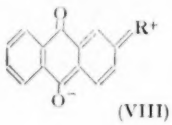
Substituent R	Band of longest wave-length: 1-R-Anthraquinone * in MeOH	1-R-Anthraquinone * in *o*-C_6H_4Cl·OH	2-R-Anthraquinone * in MeOH	2-R-Anthraquinone * in *o*-C_6H_4Cl·OH	Substituent R	Band of longest wave-length: 1-R-Anthraquinone * in MeOH	1-R-Anthraquinone * in *o*-C_6H_4Cl·OH	2-R-Anthraquinone * in MeOH	2-R-Anthraquinone * in *o*-C_6H_4Cl·OH
NO_2	—	—	~420 (ca. 50)	—	NHMe	503 (7,100)	—	462 (5,700)	—
CN	~417 (ca. 70)	—	~413 (ca. 100)	—	O^-	493 (5,000)	—	465 (5,400)	—
Cl	~415 (ca. 100)	—	—	—	NMe_2	503 (4,900)	—	472 (5,900)	—
H	~410 (ca. 60)	—	~410 (ca. 60)	—	NHAc	400 (5,600)	414 (5,000)	367 (4,200)	—
Me	~415 (ca. 150)	—	—	—	NHBz	405 (6,400)	424 (6,200)	—	375 (6,900)
OMe	378 (5,200)	—	363 (3,950)	—	NMeAc	—	ca. 337 (ca. 5,000)	—	—
OH	402 (5,500)	—	368 (3,900)	—	NMeBz	—	ca. 335	—	—
NH_2	475 (6,300)	488 (6,400)	440 (4,500)	445 (6,400)					

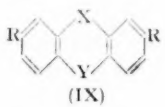
* See footnote to Table I.

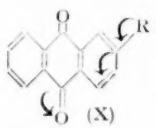
However, the principal difference between electron-attracting and electron-donating substituents lies in the effect on the visible absorption spectrum. The former do not alter appreciably the small visible absorption of anthraquinone (Table 2), from which it may be

concluded that they do not develop a new fundamental oscillation, but merely modify those already present. On the other hand, electron-donating substituents cause very marked changes which completely overshadow those in the ultra-violet region; the principal change is development of an absorption band in, or overlapping, the visible region of the spectrum, and this must be regarded as a fundamental band arising from electronic oscillations in the molecule as a whole.

The wave-length of maximum visible absorption increases in the order OH, NH_2, O^-, NHMe (Table 2), which is also the order of increasing electromeric possibilities of these groups. Lewis (*J. Amer. Chem. Soc.*, 1945, **67**, 770) similarly showed that for dyes of the type (IX), when X and Y are constant, $\lambda_{max.}$ increased along the series R = OH, OR, NH_2,


(VIII)


(IX)


(X)

O^-, NR_2, owing to changes in the contributions of the optically important ionic structures; and Doub and Vandenbelt (*ibid.*, 1947, **69**, 2714) observed that the position of the primary band of benzene underwent an increasing bathochromic shift along the series H, OH, Me, NH_2, and associated this shift with the displacement of electrons to or from the benzene ring depending on the electron-attracting or -donating power of the group. For 2-substituted anthraquinones (Table 2) $\lambda_{max.}$ of the band of longest wave-length increases in the order of $OH < NH_2 < NHMe \leqslant O^- < NMe_2$, which can be connected with electron-donation into the anthraquinone nucleus as shown in (X). It follows that if the auxochrome is modified by a group which tends to attract electrons the absorption band will be moved to shorter wave-lengths. In the naphthaquinone series Spruit and Morton and Earlam (*locc. cit.*) demonstrated that acetylation of 1-hydroxy-naphtha- and -anthra-quinone entirely suppressed the visible band, the spectrum reverting to that of the unsubstituted quinone, but with more intense absorption. Similarly acetylation or benzoylation of 1- or 2-aminoanthraquinone causes a large hypsochromic shift in the visible band (Table 2). The electromeric effect may also be suppressed by immobilising the lone pair of electrons on the nitrogen atom as hydrochloride, the visible peaks in methanol solution being diminished and finally completely suppressed by the addition of increasing amounts of hydrogen chloride.

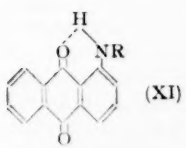
One anomaly must, however, be mentioned. On the grounds of electromeric effects the wave-length associated with a methoxyl should be greater than that associated with a hydroxyl group, the methyl group increasing the effect. Doub and Vandenbelt showed that the change in wave-length of the primary band of benzene is greater for methoxyl than for hydroxyl; however, later work by Robertson, Seriff, and Matsen (*J. Amer. Chem. Soc.*, 1950, **72**, 1539) on the longer wave-length absorptions of these compounds shows that phenol absorbs at longer wave-lengths than anisole (approx. 273 and 271 mμ respectively), and they interpreted this as being due to the oxygen atom having a higher electron density when a hydrogen atom is attached to it than when an alkyl group is present, as is shown by the bond dipole moments of 1·5 D for hydroxyl and 0·8 D for methoxyl. Thus, it seems probable that the hydroxyl group would resonate more with the benzene nucleus than would the alkoxyl group, and absorption would then occur at longer wave-lengths. In a further paper Robertson and Matsen (*ibid.*, p. 1543) show that, for aniline, introduction of *N*-methyl groups has the reverse and, on the basis of electronic theory, the expected effect: *i.e.*, the absorption is moved towards the visible region and it is suggested that the lower electronegativity of nitrogen permits the alkyl groups to enter into resonance with the aniline nucleus to a greater extent than in anisole. Analogously, Dannenburg (*Z. Naturforsch.*, 1949, **4***b*, 327) showed that the wave-lengths of maximum absorption of *p*-hydroxybenzoic acid and *p*-hydroxyacetophenone are greater than for the corresponding methoxy-derivatives; and again for 2-substituted anthraquinones (Table 2) the bands of longest wave-length fall in the order OMe, OH, NH_2, NHMe, O^-, NMe_2.

1-Substituted anthraquinones show further anomalies, namely, that $\lambda_{max.}$ should be greater for NMe_2 than for NHMe, and greater for NMeAc than for NHAc. Here two explanations are possible, depending on the presence of intramolecular hydrogen bonding or steric interactions within the molecule.

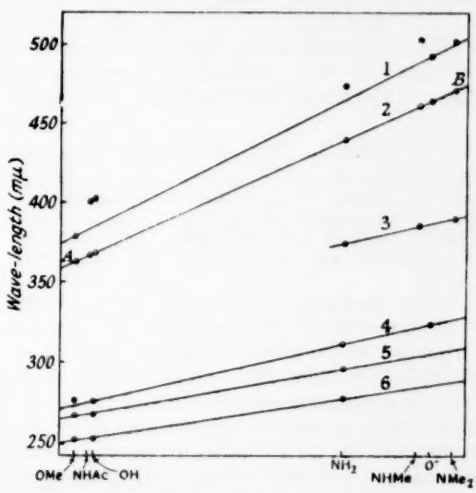
Now there is, in a large number of cases, a hydrogen atom in the substituent which in the 1-substituted anthraquinones is able to form a hydrogen bond, as in (XI; R = H or acyl). The resultant possibilities of further resonance will alter the colour of the compound. Such mechanisms have been suggested by others for 1-hydroxy-naphtha- and -anthraquinones, and their effect may be shown most easily by a correlation of the Hixon–Johns type (*J. Amer. Chem. Soc.*, 1927, **49**, 1786). In Fig. 1 an arbitrary straight line *AB* is drawn whose ordinate scale represents the wave-length of maximum absorption, the absicssa being undefined. The points corresponding to the $\lambda_{max.}$ of the 2-R-anthraquinones, where R is an electron-donating substituent, are marked on this line, and an arbitrary scale of abscissae is then constructed labelled with the names of the substituents. Plots of the measured $\lambda_{max.}$ of *para*-substituted benzoic acids, acetophenones, and nitrobenzenes,

FIG. 1.

1, 1-R-*Anthraquinone in* MeOH.
2, 2-R-*Anthraquinone in* MeOH.
3, p-R-*Nitrobenzene in* EtOH.
4, p-R-*Acetophenone in* H_2O.
5, p-R-*Acetophenone in* Et_2O.
6, p-R-*Benzoic acid in* Et_2O.



(XI)



respectively due to Dannenburg (*loc. cit.*), Doub and Vandenbelt (*loc. cit.*), and Kumler (*ibid.*, 1946, **68**, 1184), on the scale of substituents so defined, also show linear relations, confirming the validity of this abscissa scale. However, $\lambda_{max.}$ of the 1-R-anthraquinones, plotted against the same scale, do not approximate to a straight line. In this case if those substituents are chosen where interaction is unlikely, that is O^- and OMe, and a line is drawn through these points, all the derivatives which have internal-hydrogen-bonding possibilities lie above the line. This suggests that they have a $\lambda_{max.}$ greater than would be expected from their electron-donating capabilities, the excess being attributable to the resonance possibilities developed by the formation of the chelate structure.

Further evidence for the presence of such intramolecular hydrogen bonds is found in calorimetric data of Doherty, Grimshaw, Longster, and Nicholson (personal communication), to the effect that, for the 1-hydroxy-, 1-amino-, and 1-methylamino-anthraquinone, the heats of sublimation and resonance energies suggest the presence of such bonds, whereas in 2-aminoanthraquinone the bonds are intermolecular. Chaplin and Hunter (*J.*, 1938, 375) similarly found that 1-acetamidoanthraquinone did not aggregate in solution, this being attributed to the presence of the chelate structure, whilst the 2-derivatives formed aggregates. The basic dissociation constants of amino- and *N*-substituted amino-anthraquinones in methanol (Peters and Sumner, unpublished work; Table 3) show a markedly higher basic strength for the 2- than for the corresponding 1-derivatives, which can again be correlated with intramolecular hydrogen bonding. Hydroxyanthraquinones

show a similar effect (Huttig, *Z. physikal. Chem.*, 1914, **87**, 129), the dissociation constant being $3{\cdot}2 \times 10^{-12}$ and $2{\cdot}4 \times 10^{-8}$ for the 1- and 2-derivative respectively.

If hydrogen bonding is eliminated by methylation, $\lambda_{max.}$ should fall into line with the electron-donating powers of the group, and this is found to be so for the 1-dimethylaminoanthraquinone (Fig. 1). By a similar mechanism the acetyl and benzoyl derivatives of 1-methylaminoanthraquinone absorb at shorter wave-lengths than the corresponding derivatives of 1-aminoanthraquinone, but it also appears likely that here the second possibility of steric hindrance must be considered.

Molecular models show that there is marked steric hindrance between these substituents and the rest of the molecule for the 1-substituted anthraquinones, which will reduce the mesomeric effect by preventing the molecule from taking up a planar configuration. Classical examples are in the diphenyl series (Ferguson, *Chem. Reviews*, 1948, **43**, **421**; Beaven, Hall, Lesslie, and Turner, *J.*, 1952, 854). Similarly, steric hindrance may occur between large 1-substituents and the keto-oxygen atom, the result being to twist the group out of the position relative to the anthraquinone nucleus in which the maximum mesomeric possibilities can occur. Such is the case for 1-dimethylaminoanthraquinone where, although the wave-length of maximum absorption accords with the mesomeric capabilities of the group, the extinction coefficient is considerably reduced (Table 2). Again, it is of interest that the basic strength of 1-dimethylaminoanthraquinone is markedly higher than those of the amino- and methylamino-derivatives (Table 3), as follows from consider-

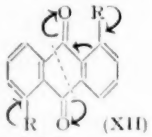
TABLE 3. *Basic dissociation of aminoanthraquinones in methanol.*

Substituent	Basic dissoc. const.	Substituent	Basic dissoc. const.	Substituent	Basic dissoc. const.
1-NH_2	$8{\cdot}1 \times 10^{-17}$	2-NH_2	$7{\cdot}4 \times 10^{-16}$	1 : 5-$(NH_2)_2$ (1st dissoc.)	ca. 2×10^{-16}
1-NHMe	$2{\cdot}9 \times 10^{-17}$	2-NHMe	$1{\cdot}1 \times 10^{-16}$	1 : 4-$(NH_2)_2$ (1st dissoc.)	$4{\cdot}9 \times 10^{-15}$
1-NMe_2	ca. 5×10^{-13}	2-NMe_2	$6{\cdot}1 \times 10^{-17}$		

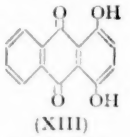
ation of the resonance of the amino-group with the nucleus. *E.g.*, aniline is a much weaker base than methylamine, a fact which is attributed to the mesomeric shift of electrons from the amino-group to the benzene ring in the former compound. If the amino-group is out of the plane of the aromatic nucleus, as is the case for 1-dimethylaminoanthraquinone, the conjugation is reduced and the group tends to exert its normal basicity.

Summarising, it has been shown that the visible colour of the simple monosubstituted anthraquinones can be attributed to the mesomeric drift of electrons from the substituent to the nucleus. The effect of this drift in producing visible colour is assisted by the formation of new resonance possibilities due to intramolecular hydrogen bonding, and suppressed by steric hindrance which prevents the full electron-donating properties of the substituent from being effective.

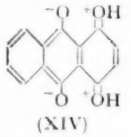
Disubstituted Anthraquinones.—Although the absorption band in the visible region of the spectrum has been attributed to resonance between the nucleus and the substituent, in some of the disubstituted anthraquinones there is evidence that this band does not necessarily arise from the molecule as a whole, but only from a part of it. Thus the intensities at any wave-length for 1 : 8- and 1 : 5-dihydroxyanthraquinone are approximately



(XII)



(XIII)



(XIV)

twice those for the 1-hydroxy-compound (Spruit, *loc. cit.*). This would arise if, as suggested previously, the band was associated with the conjugation of the substituent with the keto-group, that is, the molecule would than be divided diagonally, as in (XII). The 1 : 4-derivatives show no such simple additivity, owing, no doubt, to interaction between the two chromophoric systems, probably producing a new one. Thus, in 1 : 4-dihydroxyanthraquinone, interaction may occur giving resonance, the extreme structures being (XIII)

and (XIV). Similar considerations apply to the 1 : 4-diamino-compound. This difference in behaviour of the 1 : 4-diamino-compounds has been discussed by Allen, Wilson, and Frame (*loc. cit.*) who point out that the simple 1 : 4-disubstituted anthraquinones have a " double-headed " peak which is not shown by the 1- or 1 : 5-compounds. They attribute this to a two-fold mesomeric shift of electrons from the substituents.

These effects are evident in the spectra of 1-amino-, 1-acetamido-, and 1-benzamido-anthraquinone, and the corresponding 1 : 5-derivatives. In all cases, the 1 : 5-compound has a spectrum which is approximately double that of the monosubstituted derivative, whereas the 1 : 4-disubstituted anthraquinones show a marked shift in peak absorption to longer wave-lengths (Fig. 2, and Table 4). Further, the basic dissociation constants of substituted 1-aminoanthraquinones fall into line with the concept of the separation of the chromophoric system of 1 : 5- but not of 1 : 4-disubstituted anthraquinones. Introduction

FIG. 2.

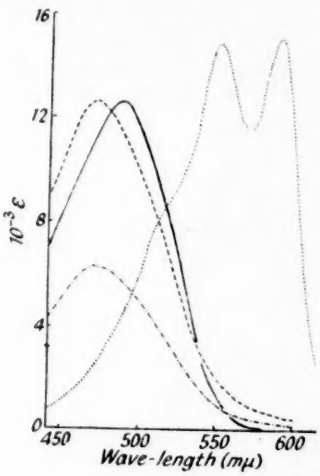


FIG. 3. *Effect of acid on* 1 : 4-*diaminoanthraquinone.*

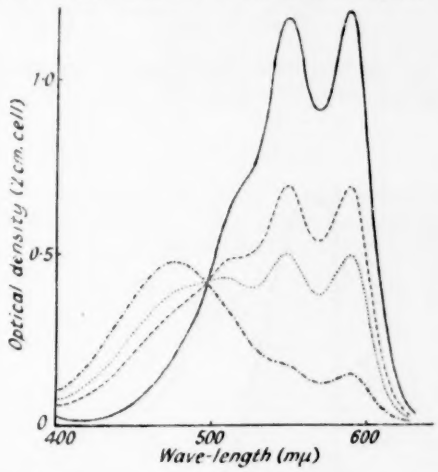


FIG. 2. — · — · — 1-*Aminoanthraquinone.*
——— *Ditto, but with* ε × 2.
——— 1 : 5-*Diaminoanthraquinone.*
——— 1 : 4-*Diaminoanthraquinone.*
(*Solutions in* MeOH.)

FIG. 3. ——— 1 : 4-*Diaminoanthraquinone in methanol* (0·00966 *g./l.*).
——— } *As above plus hydrogen chloride.*
— · — · — }

of substituents in the 5-position causes changes in the dissociation constant which are much less marked than with the same substituent in the 4-position; compare the results for the 1-amino-, 1 : 5-diamino-, and 1 : 4-diamino-anthraquinone quoted in Table 3.

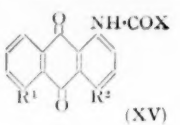
Again, as for the monosubstituted derivatives, if electron-attracting groups are introduced by acetylation or benzoylation of the amino-compounds, a shift of $\lambda_{max.}$ to shorter wave-lengths occurs (Table 4). It is worthy of note that, in these instances, the usual

TABLE 4. *Solutions in o-chlorophenol.*

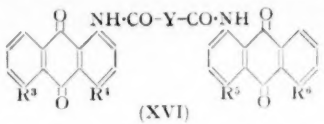
Anthraquinone derivative	Peak wave-length ($\lambda_{max.}$, mμ)	ε	2 × ε	Anthraquinone derivative	Peak wave-length ($\lambda_{max.}$, mμ)	ε	2 × ε
1-NH_2	488	6,400	12,800	1-NHBz	424	6,100	12,200
1 : 5-$(NH_2)_2$ ...	500	11,900	—	1 : 5-$(NHBz)_2$	445	11,500	—
1 : 4-$(NH_2)_2$ ...	596 554	13,800 13,400	—	1 : 4-$(NHBz)_2$	488	7,100	—
1-NHAc	414	5,000	10,000				
1 : 5-$(NHAc)_2$ ...	435	9,700	—				
1 : 4-$(NHAc)_2$ ...	474	6,700	—				

double-headed peak of the 1 : 4-derivatives does not appear. The effect of *N*-methylation is the same as in the monobenzamido-derivative, 1 : 4-bis-*N*-methylbenzamidoanthraquinone having no peak in the visible region. Again, addition of acid to a methanolic solution of 1 : 4-diaminoanthraquinone results in development of an absorption band at the wave-length of 1-aminoanthraquinone owing to formation of the monohydrochloride and suppression of the effect of one of the amino-groups (Fig. 3).

Chromophoric Insulation.—The absorption spectra of a series of acylated aminoanthraquinones of types (XV) and (XVI) are given in Table 5 and Figs. 4, 5, and 6, where the molar extinction coefficients are plotted against wave-length. In these compounds Y may be (*a*) $-[CH_2]_n-$, or a phenyl group linked (*b*) in the *meta*- or (*c*) in the *para*-positions.



(XV)



(XVI)

In type (*a*), the absorption spectra of compounds (XVI) are double those of the corresponding derivatives (XV) when $R^1 = R^3 = R^6$, $R^2 = R^4 = R^5$, and X = Me (in some

FIG. 4.

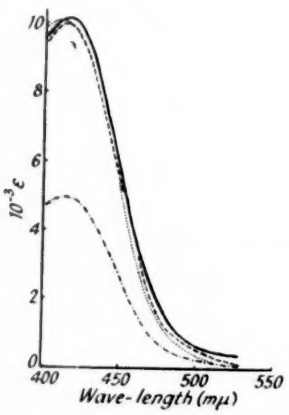


FIG. 5.

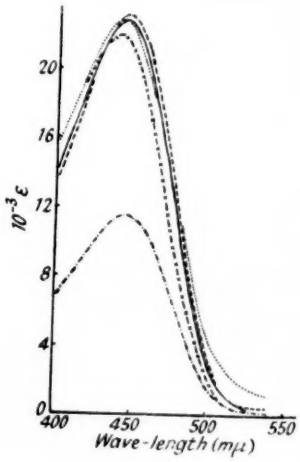


FIG. 4. —·—·—·— 1-*Acetamidoanthraquinone.*
——— *Ditto, but with* ε × 2.
——— (XVI; $R^3 = R^4 = R^5 = R^6 = H$, $Y = [CH_2]_2$).
——— (XVI; $R^3 = R^4 = R^5 = R^6 = H$, $Y = [CH_2]_4$).
(*Solutions in* o-C_6H_4Cl·OH.)

FIG. 5. —·—·—·— 1 : 5-*Dibenzamidoanthraquinone.*
——— *Ditto, but with* ε × 2.
——— (XVI; $R^4 = R^5 = H$, $R^3 = R^6 = NHBz$, $Y = m$-C_6H_4).
——— (XVI; $R^4 = R^5 = H$, $R^3 = R^6 = NHBz$, $Y = p$-C_6H_4).
— × — × — (XVI; $R^4 = R^5 = H$, $R^3 = R^6 = NHBz$, Y = —).
(*Solutions in* o-C_6H_4Cl·OH.)

cases values of *n* from 1 to 8 have been considered) (see Fig. 4 and Table 5). Such a series of compounds is analogous to those given by Piper and Brode (*J. Amer. Chem. Soc.*, 1935, **57**, 135), showing again that methylene groups behave as excellent chromophoric insulators. Comparable sets of type (*b*) give similar results. For example, the spectrum of the *iso*-phthaloyl compound (XVI; Y = *m*-C_6H_4, $R^4 = R^5 = H$, $R^3 = R^6 = NHBz$) is twice that of 1 : 5-dibenzamidoanthraquinone (XV; X = Ph, $R^1 = NHBz$, $R^2 = H$). Two examples of this series are given in Figs. 5 and 6, and show that the *m*-phenylene group acts as a chromophoric insulator.

If the group Y is a *p*-phenylene residue the additivity still occurs, though it is possible to form a conjugated system of double bonds across the benzene ring (Fig. 5). Similarly, joining the two anthraquinone nuclei by means of the oxalyl group does not influence the

TABLE 5. *Solutions in o-chlorophenol.*

Compound (XV)			Compound (XVI)			Max. absorption,		
R^1	R^2	X	$R^3 = R^6$	$R^4 = R^5$	Y	$\lambda_{max.}$, mμ	ε	2 × ε
H	H	Me				414	5,000	10,000
			H	H	$[CH_2]_2$	415	10,100	—
			H	H	$[CH_2]_4$	411	10,100	—
H	NHBz	Me				480	7,000	14,000
			H	NHBz	$[CH_2]_4$	484	14,400	—
NHBz	H	Me				440	10,600	21,200
			NHBz	H	$[CH_2]_2$	441	21,200	—
			NHBz	H	—	440	21,900	—
H	H	Ph				424	6,100	12,200
			H	H	*m*-C_6H_4	419	11,600	—
			H	H	*p*-C_6H_4	420	12,600	—
H	NHBz	Ph				488	7,100	14,200
			H	NHBz	*m*-C_6H_4	485	13,000	—
			H	NHBz	*p*-C_6H_4	485	13,000	—
NHBz	H	Ph				445	11,500	23,000
			NHBz	H	*m*-C_6H_4	444	22,800	—
			NHBz	H	*p*-C_6H_4	442	22,800	—
$R^3 = R^5 = H$, $R^4 = R^6 = NHBz$					*m*-C_6H_4	451	14,800	—

additivity (Fig. 5). The insulating effect of the *p*-phenylene group is readily explained. In a compound *p*-X·C_6H_4·CHO, conjugation of the benzene ring with the carbonyl group is restrained by the presence of an electron-attracting (+ *E*) substituent in the *para*-position.

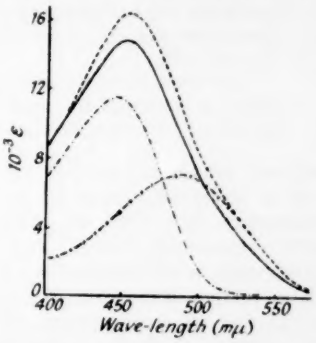


FIG. 6.

— · — · — 1 : 5-*Dibenzamidoanthraquinone* (*A*).
— × — × — 1 : 4-*Dibenzamidoanthraquinone* (*B*).
— — — — *Algebraic sum of* (*A*) *and* (*B*).
——— (XVI; $R^3 = R^5 = H$, $R^4 = R^6 =$ NHBz, Y = *m*-C_6H_4).

In the case under consideration therefore, the benzene residue between the two strongly electron-attracting carbonyl groups takes little or no part in the conjugation. Similarly, in the oxalyl derivative, the bond between the carbonyl groups will be stabilised, and as such will prevent conjugation between the two halves of the molecule.

It is possible to cause small changes in the wave-lengths of maximum absorption of the benzamidoanthraquinones by substitution in the benzoyl group (Table 6). Electron-

TABLE 6. *Anthraquinone derivatives.*

Substituent in NHBz	1-NHBz in pyridine		1 : 4-$(NHBz)_2$ in *o*-C_6H_4Cl·OH		1 : 5-$(NHBz)_2$ in *o*-C_6H_4Cl·OH	
	$\lambda_{max.}$ (mμ)	ε	$\lambda_{max.}$ (mμ)	ε	$\lambda_{max.}$ (mμ)	ε
p-NO_2	407	6500	—	—	—	—
m-NO_2	408	6050	—	—	—	—
p-Cl	417	6400	487	7300	445	11,800
m-Cl	415	6100	483	6700	444	10,700
H	415	6350	488	7100	445	11,500
p-Me	420	6500	493	6980	449	11,200
m-Me	419	6250	490	7020	446	11,200
p-OMe	424	6200	498	6940	454	11,600
m-OMe	—	—	—	—	446	11,600

attracting substituents, which decrease the amount of conjugation, cause a greater mesomeric drift of electrons from the nitrogen atom to the carbonyl group, and thus less to the nucleus. This is shown in a hypsochromic shift in $\lambda_{max.}$. The reverse is found to be true for electron-donating substituents. It is of interest, however, that the hypsochromic changes due to electron-attracting groups are relatively small. This suggests that an unsubstituted benzene ring is already partaking to the minimum possible extent in the conjugation within the molecule.

Experimental.—The compounds used were recrystallised several times from suitable solvents. The absorption spectra in solution were measured in the visible region (400—700 mμ) by means of a General Electric, and in the ultra-violet by a Cary, Recording Spectrophotometer. The solvents were dried and distilled to spectroscopic quality.

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431. *Reaction of Indane and Tetralin with Excess of Acetylating Agent.*

By G. BADDELEY, E. WRENCH, and (in part) R. WILLIAMSON.

5-Acetylindane and 6-acetyltetralin, the products of Friedel–Crafts acetylation at room temperature, react readily with acetylating agent above 70°; they provide (*a*) 2 : 5- (I) and 2 : 6-diacetylindene (II), and (*b*) 6 : 3-diacetyl-1 : 2-dihydronaphthalene (VI) respectively. 4-*p*-Acetylphenylbut-3-en-2-one (V) has been prepared by acetylation of *p*-acetylstyrene, and its ultra-violet absorption spectrum has been compared with the spectra of (I), (II), and (VI).

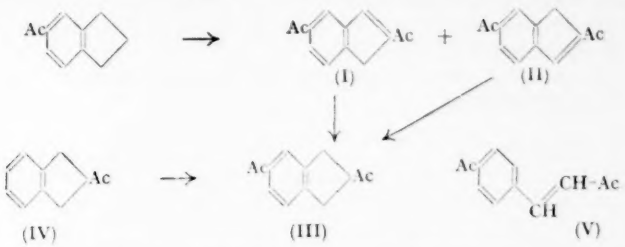
The mechanism of interaction of acylating agent and alicyclic hydrocarbon is discussed and applied to the acylation of 5-acetylindane, 6-acetyltetralin, 9 : 10-dihydroanthracene, and *cyclo*hexane.

INDANE and tetralin are readily acetylated by acetyl chloride or acetic anhydride in the presence of aluminium chloride; the products, 5-acetylindane (von Braun, Kirschbaum, and Schumann, *Ber.*, 1920, **53**, 1155) and 6-acetyltetralin (Barbot, *Bull. Soc. chim.*, 1930, **47**, 1314) respectively, like all aryl ketones in which mesomeric interaction of aryl and carbonyl groups is not inhibited by bulky substituents in the *o*- and *o'*-positions, cannot be acetylated further in the aromatic ring, nor are they affected by fusion with excess of aluminium chloride at temperatures up to 170°. These considerations, together with the knowledge that acetylating agents react with aliphatic and alicyclic hydrocarbons, made it appear possible that reaction of acetylating agent with the non-aromatic rings of the above ketones could be enforced; this has been realised.

Tetralin was gradually added to a mixture of acetyl chloride (3 mol.) and aluminium chloride (4 mol. as $AlCl_3$) in ethylene dichloride at room temperature; after 6-acetyltetralin had been formed further ready evolution of hydrogen chloride occurred only above 70°. Solvent was removed under reduced pressure and the residue, after 2 hours at 100°, gave 3 : 6-diacetyl-1 : 2-dihydronaphthalene (VI). When applied to indane this procedure gave a mixture of 2 : 5- (I) and 2 : 6-diacetylindene (II). In the presence of solvent, these products are also obtained after reaction for 2 hours at 75° or for several days at room temperature.

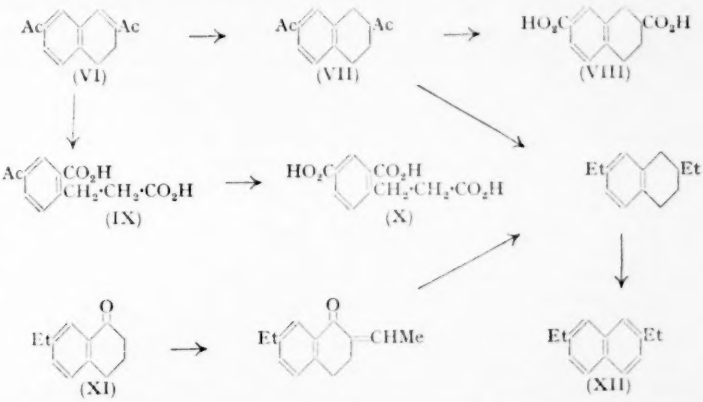
In ethanolic sodium ethoxide, (I) isomerised to (II), and catalytic hydrogenation of each gave 2 : 5-diacetylindane (III), identical with the product of acetylation of 2-acetylindane (IV). The identity of the two, isomeric diacetylindenes is established by a comparison of their absorption spectra with those of 4-*p*-acetylphenylbuten-2-one (V), benzylideneacetone, and 4-acetylstyrene (XIII), as recorded in the Table. The absorption spectrum of 3 : 6-diacetyl-1 : 2-dihydronaphthalene (VI) is similar to that of (I). The constitution of (VI) was established (*a*) by conversion into 2 : 7-diacetyl-1 : 2 : 3 : 4-tetrahydronaphthal-

ene (VII) (no absorption at 300 mμ), followed by oxidation with selenium dioxide to tetralin-2 : 7-dicarboxylic acid (VIII) or reduction and dehydrogenation to 2 : 7-diethyl-



naphthalene (XII), and (*b*) by oxidation successively with permanganate and hypochlorite to the acids (IX) and (X). An authentic sample of (XII) was prepared from 7-ethyl-1-tetralone (XI).

	$\lambda_{max.}$ (Å)	ε	$\lambda_{max.}$ (Å)	ε
2 : 6-Diacetylindene (II)	3050	25,800	—	—
2 : 5- ,, (I)	2950	22,000	2550	23,000
2 : 5-Diacetylindane (III)	—	—	2550	13,400
4-Acetylstyrene (XIII)	2800	21,500	—	—
Benzylideneacetone	2860	23,440	—	—
4-*p*-Acetylphenylbut-3-en-2-one (V)	2950	29,500	—	—
3 : 6-Diacetyl-1 : 2-dihydronaphthalene (VI)	3000	16,600	2600	32,500
2 : 7-Diacetyl-1 : 2 : 3 : 4-tetrahydronaphthalene (VII)	—	—	2500	12,000



4-*p*-Acetylphenylbut-3-en-2-one (V), which was needed for comparison, could not be obtained by acetylation of benzylideneacetone or styrene; the former was not acetylated and the latter was polymerised (Bachmann *et al.*, *J. Org. Chem.*, 1947, **12**, 108). It was readily prepared by acetylation of acetylstyrene, which was obtained by acetylation of 2-phenylethyl chloride under carefully selected conditions (see Experimental section) and subsequent dehydrochlorination with triethanolamine. Its structure was established by catalytic hydrogenation to a dihydro-derivative which is 2-*p*-acetylphenylethyl methyl ketone (XIV) since it is identical with the product of acetylation of methyl 2-phenylethyl ketone :

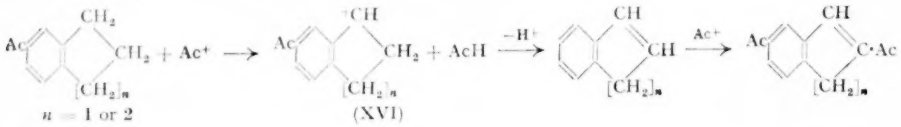
$$C_6H_5\cdot CH_2\cdot CH_2Cl \longrightarrow p\text{-}Ac\cdot C_6H_4\cdot CH_2\cdot CH_2Cl \longrightarrow p\text{-}Ac\cdot C_6H_4\cdot CH{=}CH_2 \ (XIII) \longrightarrow$$

$$p\text{-}Ac\cdot C_6H_4\cdot CH{:}CHAc \ (V) \longrightarrow p\text{-}Ac\cdot C_6H_4\cdot CH_2\cdot CH_2Ac \ (XIV) \longleftarrow C_6H_5\cdot CH_2\cdot CH_2Ac$$

$$p\text{-}O{=}CMe\text{—}C_6H_4\text{—}CH{=}CH_2 \quad (XV)$$

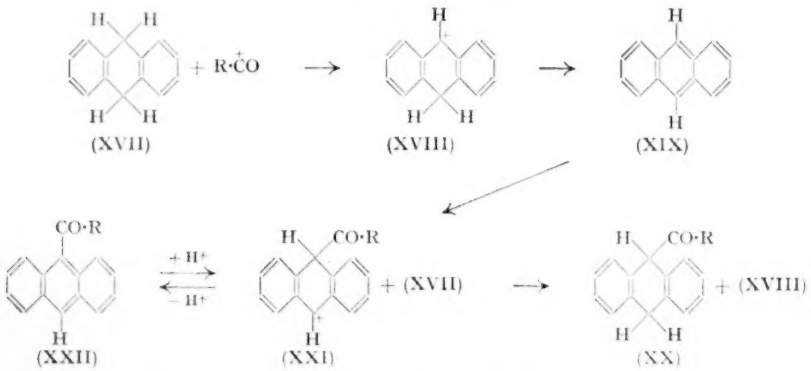
It is noteworthy that the acetyl group of *p*-acetylstyrene lowers the electron density at the vinyl group (as shown in XV) sufficiently to prevent polymerisation in the presence of acetylating agent, while, at the same time, the *p*-acetylphenyl group is sufficiently polarisable to provide an electromeric release of electrons (shown in XIII) which enables acetylation to occur at the terminal carbon atom.

Interaction of excess of acetylating agent and 5-acetylindane or 6-acetyltetralin is best represented by the scheme:



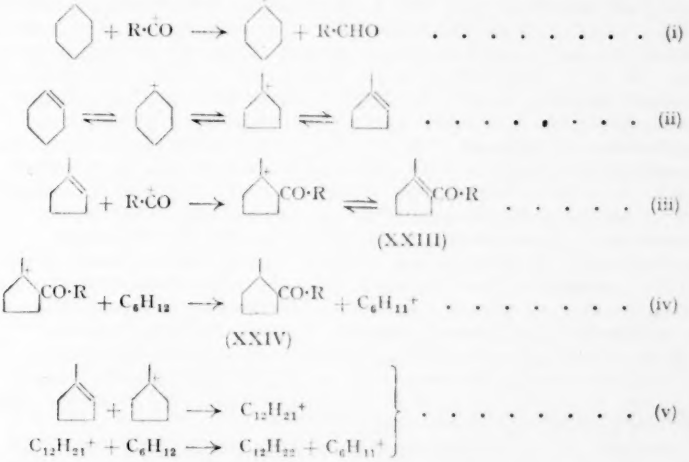
Loss of hydride ion to acetyl cation occurs at a methylene group adjacent to the benzene ring since, in this way, resonance stabilisation of the resulting carbonium ion (XVI) is best effected. This stabilising effect requires release of electrons from the benzene ring and, therefore, the methylene group in the *meta*-position to the acetyl group is the one affected. The subsequent steps are self-explanatory. (XVI; $n = 2$), unlike the *cyclo*hexyl cation (see below), does not rearrange; this difference is probably due to spread of the positive charge into the aromatic ring. When $n = 1$, the product, 2 : 5-diacetylindene, readily affords the 2 : 6-isomer by migration of a proton.

Direct acylation of a methylene group seems to occur in 9 : 10-dihydroanthracene (XVII) since the 9-acyl derivative (XX) is obtained. In fact, the reaction is best represented by the annexed scheme in which reaction is initiated by transfer of hydride ion from (XVII) to acyl cation, a ready process as the charge on (XVIII) is spread over two benzene rings, and formation of anthracene (XIX). A chain reaction then ensues: (XIX) affords 9-acetylanthracene (XXII) which, as the cation (XXI), is reduced to (XX) by gain of hydride ion from (XVII). This scheme is supported by the fact (see Experimental section) that a mixture of (XVII), (XXII), and aluminium chloride affords (XIX) and (XX).



These considerations can, by suitable modification, be applied to the acylation of aliphatic and alicyclic hydrocarbons. The following scheme, in which the hydrocarbon is *cyclo*hexane, is analogous to that for reaction of alkyl cation with saturated hydrocarbons (Schmerling, "Catalytic Reactions of Hydrocarbons—Ionic Mechanism," Symposium No. 24, Sept, 1952, New Jersey). Reaction (i) accounts for the formation of aldehyde (cf. Nenitzescu *et al.*, *Annalen*, 1931, **491**, 189; *Ber.*, 1932, **65**, 1449) and, like (iv), involves transfer of hydride ion. Reaction (ii) represents interconversion of *cyclo*hexene and 1-methyl*cyclo*pentene (Adkins and Roebuck, *J. Amer. Chem. Soc.*, 1948, **70**, 4041) and includes the same isomerisation of *cyclo*alkyl cations as occurs in the interconversion of *cyclo*hexane and methyl*cyclo*pentane (Pines, Abraham, and Ipatieff, *ibid.*, 1948, **70**, 1742).

Reaction (iii) suitably represents the acylation of 1-methyl*cyclo*pentene. Combination of (iv) with the right-hand side of (iii) illustrates reduction of αβ-unsaturated ketone by *cyclo*hexane, and several reductions of this type are known; *e.g.*, interaction of *cyclo*hexene, crotonyl chloride, and aluminium chloride in *cyclo*hexane affords saturated ketone, *cyclo*hexyl *n*-propyl ketone (Nenitzescu and Curcaneanu, *Bull. Soc. chim. Romania*, 1939,



1, 133), and an unsaturated ketone (*cyclo*hexenyl propylidene ketone), together with its products of hydrochlorination, in inert solvents (Baddeley, Taylor, and Pickles, *J.*, 1953, 124). This reduction process readily accounts for variation of relative amounts of saturated and unsaturated ketone with experimental procedure; *e.g.*, Telinsky and Tarassowa (*Ber.*, 1932, **65**, 1249; *Annalen*, 1934, **508**, 115) showed that acetylation of *cyclo*hexane at 18—35° provides mainly (XXIII), whereas, when the temperature is gradually raised to 70°, the product is almost entirely (XXIV).

Experimental

Tetralin and Excess of Acetylating Agent.—(i) *In ethylene chloride.* At room temperature, a mixture of tetralin (16 g.), acetyl chloride (32 g., 2 mol.), and aluminium chloride (56 g., 2 mol.) in ethylene dichloride (40 c.c.) rapidly evolved hydrogen chloride (1 mol.) and gave 6-acetyltetralin. Hydrogen chloride was again rapidly evolved when the mixture was warmed to 70—75° and this reaction was complete after 2 hr. The mixture was worked up in the usual way and gave 6-acetyltetralin (20 g.), b. p. 165—175°/15 mm., and 3 : 6-*diacetyl*-1 : 2-*dihydronaphthalene* (VI) (7 g.), b. p. 190—200°/0·12 mm., needles (from light petroleum), m. p. 73—74°, together with unsaturated material of intermediate b. p. These products (20 and 10 g. respectively) were also obtained after reaction for 3 days at 20°. Tetralin (25 g.), acetic anhydride (61 g., 2 mol.), and aluminium chloride (168 g., 4 mol.) in ethylene dichloride at 70—75° gave the same products (14·6 and 13·5 g. respectively).

(ii) *Without solvent.* Tetralin (26 g.) was gradually added to a mixture of aluminium chloride (112 g., 4 mol.) and acetyl chloride (48 g., 3 mol.) in ethylene chloride (75 c.c.). When vigorous reaction at room temperature had ended, the solvent was removed under reduced pressure and the residue heated for 2 hr. at 100°. Only one fraction, b. p. 190—200°/0·12 mm. (18 g.), was obtained and this provided pure (VI) (13 g.).

6-*Acetyltetralin and Acetylating Agent* (1 *mol.*).—Since addition of aluminium chloride to a mixture of acetyltetralin and acetyl chloride causes extensive decomposition, the reaction mixture was prepared by adding a molten mixture of the ketone (8·7 g.) and aluminium chloride (10·5 g., 1·5 mol.) to a mixture of acetyl chloride (4·0 g., 1 mol.) and aluminium chloride (10·5 g.). After 2 hr. at 100°, the same two products (5 and 4 g. respectively) were obtained.

Identification of (VI).—(i) This *compound* (Found: C, 78·7; H, 6·6. $C_{14}H_{14}O_2$ requires C, 78·7; H, 6·55%) combined with 2 : 4-dinitrophenylhydrazine (2 mol.), affording a *bis*-2 : 4-

dinitrophenylhydrazone, red prisms (from nitrobenzene), decomp. 270° (Found: C, 54·5; H, 3·8; N, 19·6. $C_{26}H_{22}O_8N_8$ requires C, 54·4; H, 3·8; N, 19·5%). (ii) The compound (VI) (10·7 g.) in ethanol over Raney nickel absorbed hydrogen (1 mol.), giving 2 : 7-*diacetyltetralin* (VII) (9·5 g.), b. p. 180—190°/0·3 mm., plates (from light petroleum), m. p. 52—53° (Found: C, 77·6; H, 7·9. $C_{14}H_{16}O_2$ requires C, 77·75; H, 7·4%), which formed a *bis*-2 : 4-*dinitrophenylhydrazone*, orange rods (from nitrobenzene), decomp. 246° (Found: C, 54·8; H, 4·3; N, 19·9. $C_{26}H_{24}O_8N_8$ requires C, 54·2; H, 4·2; N, 19·45%). A mixture of (VII) (2·5 g.), selenium dioxide (2·5 g.), water (0·5 c.c.), and dioxan (35 c.c.) was refluxed for 4 hr.; the organic product was isolated and oxidised with hydrogen peroxide (30%; 20 c.c.) and aqueous sodium hydroxide (8%; 30 c.c.); acidification gave *tetralin*-2 : 7-*dicarboxylic acid* (VIII) (0·5 g.), m. p. 260° (decomp.) (Found: C, 65·6; H, 6·05%; equiv., 105. $C_{12}H_{12}O_4$ requires C, 65·4; H, 5·45%; equiv., 110). The acid (VIII) (1·5 g.) and palladised charcoal (30%; 0·8 g.) at 270° gave naphthalene and hydrogen (2 mol.). (iii) A mixture of (VII) (6·0 g.), amalgamated zinc (80 g.), and hydrochloric acid (*d* 1·6; 350 c.c.) was refluxed for 19 hr. and gave 2 : 7-*diethyltetralin* (2·2 g.), b. p. 150—155°/15 mm. (Found: C, 89·4; H, 10·65. $C_{14}H_{20}$ requires C, 89·4; H, 10·6%), which was dehydrogenated over palladised charcoal at 270° to 2 : 7-diethylnaphthalene; the *picrate*, m. p. and mixed m. p. (see below) 77—78°, crystallised from ethanol in orange needles (Found: C, 58·0; H, 4·8; N, 10·0. $C_{20}H_{23}O_7N_3$ requires C, 58·0; H, 4·6; N, 10·1%). (iv) Finely powdered (VI) (0·5 g.), shaken for 3 hr. with ice-cold aqueous potassium permanganate (1·0 g. in 25 c.c.), gave β-4-*acetyl*-2-*carboxyphenylpropionic acid* (IX) as radiating needles, m. p. 218—220° (from water) (Found: C, 61·5; H, 5·3%; equiv., 118. $C_{12}H_{12}O_5$ requires C, 61·5; H, 5·1%; equiv., 118). Oxidation of (IX) with alkaline hypochlorite at 100° gave β-2 : 4-dicarboxyphenylpropionic acid, m. p. 267—268° (Found: C, 55·4; H, 4·2; equiv., 79. Calc. for $C_{11}H_{10}O_6$: C, 55·4; H, 4·2%; equiv., 79); Zinke and Franke (*Annalen*, 1897, **293**, 168) give the m. p. as 265—266°.

Authentic 2 : 7-*Diethylnaphthalene*.—β-*p*-Ethylbenzoylpropionic acid was obtained by interaction of ethylbenzene, succinic anhydride, and aluminium chloride in ethylene chloride and afforded 7-ethyl-1-tetralone (Bachmann and Edgerton, *J. Amer. Chem. Soc.*, 1940, **62**, 2222; Krollpfeiffer, *Ber.*, 1923, **56**, 626). The product (19 g.) together with acetaldehyde (10 g., 2 mol.) at 0° was subjected for 3 hr. to a stream of dry hydrogen chloride and, after storage overnight, gave 7-*ethyl*-2-*ethylidene*-1-*tetralone* (17 g.), b. p. 180—185°/12 mm. (Found: C, 84·3; H, 7·8. $C_{14}H_{15}O$ requires C, 84·0; H, 8·0%). Hydrogenation over Raney nickel gave 2 : 7-diethyl-1-tetralone, b. p. 165—170°/12 mm. [*semicarbazone*, m. p. 198—199° (Found: N, 15·9. $C_{15}H_{21}ON_3$ requires N, 16·3%)], and 2 : 7-diethylnaphthalene was obtained by Clemmensen reduction.

Indane and Excess of Acetylating Agent.—(i) *In ethylene chloride at* 20°. Indane (24 g.) was added to a solution of aluminium chloride (84 g.) and acetyl chloride (48 g.) in solvent (60 c.c.); after 3 days at 20°, the mixture gave 5-acetylindane (9·3 g.), b. p. 110—120°/0·1 mm., and a mixture of 2 : 5- (I) and 2 : 6-diacetylindene (II) (10·7 g.), b. p. 180—190°/0·1 mm., which melted over a wide range.

(ii) *In absence of solvent*. The same fractions (8 and 7 g. respectively) were obtained after addition of indane (24 g.) to acetic anhydride (61 g., 3 mol.) and aluminium chloride (168 g., 6 mol.) in ethylene chloride (120 c.c.), removal of solvent under reduced pressure and heating of the residue for 2 hr. at 100°. These two fractions (7 and 15 g. respectively) were obtained by addition of indane (24 g.) to acetyl chloride (48 g.) and aluminium chloride (84 g.) and heating at 100° for 2 hr.

Identification of (I) *and* (II). (i) Mixtures of (I) and (II) were fractionally crystallised from ethanol and afforded 2 : 6-*diacetylindene* (II) as small plates, m. p. 161—163° (Found: C, 78·2; H, 6·1. $C_{13}H_{12}O_2$ requires C, 78·0; H, 6·0%), and the more soluble 2 : 5-*isomer* (I) as rods, m. p. 106—108° (Found: C, 77·8; H, 6·0%).

(ii) Both slowly decolorised aqueous permanganate and bromine in carbon tetrachloride and absorbed hydrogen (1 mol.), to provide 2 : 5-*diacetylindane* (III) (Found: C, 77·8; H, 6·8. $C_{13}H_{14}O_2$ requires C, 77·5; H, 6·9%). This was obtained in poor yield by interaction of 2-acetylindane (IV) (Perkin, *J.*, 1894, **241**) (5 g.), aluminium chloride (13 g.), and acetyl chloride (3·1 g.). (iii) Addition of ethanolic sodium ethoxide to (I) gave a deep-red solution and addition of hydrochloric acid precipitated a solid from which (II) was obtained by crystallisation from ethanol. (iv) The identity of (I) and (II) was established by comparison of their absorption spectra with those of 4-*p*-acetylphenylbuten-2-one (V), *p*-acetylstyrene (XIII), and benzylideneacetone.

2-p-*Acetylphenylethyl Chloride*.—A solution of acetyl chloride (16 g., 2 mol.) and aluminium

chloride (15 g., 1·1 mol.) in ethylene chloride was added to 2-phenylethyl chloride (13·5 g.) in ethylene chloride. Reaction was complete in a few minutes and gave the required chloride (14 g.), b. p. 168°/15 mm. The 2 : 4-*dinitrophenylhydrazone* separated from ethanol in orange-yellow needles, m. p. 184° (Found : C, 52·5; H, 4·6; N, 15·2; Cl, 9·7. $C_{16}H_{15}O_4N_4Cl$ requires C, 53·0; H, 4·2; N, 15·4; Cl, 9·8%).

p-*Acetylstyrene* (XIII).—This *compound* (6 g.), b. p. 110°/12 mm., was obtained by steam-distillation of the above chloride (10 g.), triethanolamine (100 c.c.), and water (50 c.c.); it separated from light petroleum in needles, m. p. 33° (Found : C, 81·7; H, 6·9. $C_{10}H_{10}O$ requires C, 82·1; H, 6·9%), and afforded *p*-ethylacetophenone (semicarbazone, m. p. and mixed m. p. 153°) by hydrogenation.

4-p-*Acetylphenylbut-3-en-2-one* (V).—The ketone (XIII) (1·3 g.) was gradually added to a mixture of acetyl chloride (1·0 g.) and excess of aluminium chloride in methylene chloride. Reaction was instantaneous and gave (V) (1·4 g.), as pale yellow plates, m. p. 103° (Found : C, 76·6; H, 6·2. $C_{12}H_{12}O_2$ requires C, 76·5; H, 6·5%). from light petroleum. Hydrogenation gave 4-*p*-acetylphenylbutan-2-one (XIV), b. p. 150°/0·15 mm., which was identified by its *bis*-2 : 4-*dinitrophenylhydrazone*, m. p. and mixed m. p. 272° (Found : C, 52·2; H, 4·4; N, 20·0. $C_{24}H_{22}O_8N_8$ requires C, 52·5; H, 4·0; N, 20·4%). Authentic (XIV) was prepared by addition of methyl 2-phenylethyl ketone (7·5 g.), obtained by hydrogenation of benzylideneacetone, to a mixture of acetyl chloride (4 g.) and aluminium chloride (15 g.) in methylene chloride.

Interaction of 9 : 10-*Dihydroanthracene, 9-Benzoylanthracene, and Aluminium Chloride.*—The reactants (0·7, 1·0, and 0·5 g. respectively) were brought together in carbon disulphide and set aside for 24 hr. Chromatographic separation of the products in benzene on alumina gave anthracene and 9-benzoyl-9 : 10-dihydroanthracene.

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432. *Esters containing Phosphorus. Part XI.* Ethylphosphonic Dichloride containing* ^{32}P.

By B. C. SAUNDERS and T. S. WORTHY.

Radioactive ethylphosphonic dichloride has been prepared, on a small scale in an enclosed system, by reactions not involving filtrations.

OF convenient methods for preparing non-radioactive ethylphosphonic dichloride (ethyldichlorophosphine oxide; valuable for obtaining esters of ethylphosphonic acid) two may be considered: (1) Phosphorus trichloride, ethyl chloride, and aluminium chloride form the complex $EtCl,PCl_3,AlCl_3$ which is then decomposed by hydrochloric acid (Clay, *J. Org. Chem.*, 1951, **16**, 1892; Kinnear and Perren, *J.*, 1952, 343). (2) Tetraethyl-lead converts phosphorus trichloride into ethylphosphonous dichloride (ethyldichlorophosphine) (Kharasch, Jenson, and Weinhouse, *J. Org. Chem.*, 1949, **14**, 429), which is then oxidized by sulphuryl chloride to the phosphonic dichloride (American workers, personal communication).

The first method is quicker, but the filtration entailed in this reaction presents a hazard because of the danger of inhalation when volatile radioactive materials are employed. Further this method involves some danger because of the pressure developed in an enclosed reaction vessel containing ethyl chloride. It is considered essential that work with the more volatile radioactive compounds (b. p. <150°/760 mm.), should be in a completely enclosed system. This is possible with the second method and the extra time of operation involves a decrease in the radioactivity of only 15% compared with method (1).

The volatility of phosphorus trichloride, ethylphosphonous dichloride, and sulphuryl chloride permit of their quantitative transfer in a high-vacuum system. The conversion of the phosphonous into the phosphonic dichloride was also carried out in an enclosed system.

Phosphorus trichloride was supplied by Radiochemical Centre, Amersham. The

* Part X, *J.*, 1950, 1320.

probable impurities in it are hydrogen chloride and phosphorous acid; the trichloride was obtained analytically pure by fractional evaporation and fractional condensation in the high-vacuum system. Pure ethylphosphonous dichloride was prepared according to the equation: $PbEt_4 + 3PCl_3 = 3EtPCl_2 + EtCl + PbCl_2$. The reaction vessel was attached to the high-vacuum system, and the phosphorus trichloride transferred to it without loss and without risk. Further to reduce the hazards, a powerful magnetic stirrer was employed. The ethylphosphonous dichloride was oxidized in benzene solution in a vessel (Fig. 3) connected to the vacuum system.

Since ethylphosphonic dichloride is not sufficiently volatile to allow its transfer under a high vacuum, the reaction vessel was also designed for distillation.

Experimental

Apparatus.—A high-vacuum system (Fig. 1) was used: additional apparatus could be attached to the main system by sockets J_1 and J_2. Dry air could be let into the system through

Fig. 1.

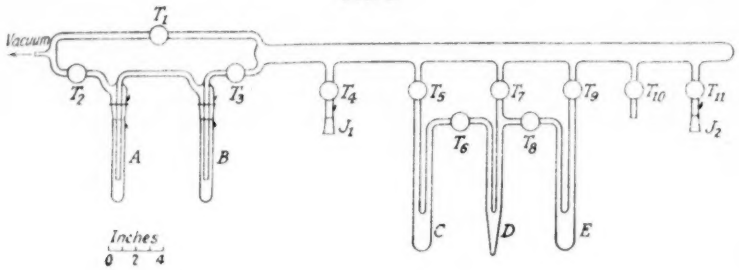


Fig. 2.

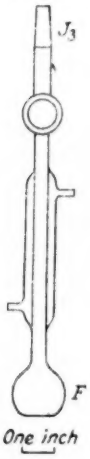
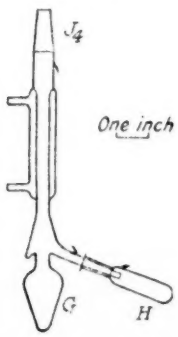


Fig. 3.



T_{10}. The system of traps *C*, *D*, *E* was used in the fractionation of phosphorus trichloride. *D* was graduated and could be used for measuring the volume of a volatile liquid in the system. The main system could be evacuated *via* T_2 and T_3 (volatile materials collecting in traps *A* and *B*) or *via* T_1.

The reaction vessel (Fig. 2) had a partially flattened base to ensure efficient magnetic stirring by a small piece of soft iron sealed in glass. It could be attached to the main system by J_3. The distillation vessel (Fig. 3) had a 15-ml. tapered flask *G*, and could be attached to the main system by J_4.

Purification of Phosphorus Trichloride.—Radioactive phosphorus trichloride (*ca.* 1 ml.; activity, 10 mc), contained in tube attached to J_2, was transferred to *E* under a high vacuum.

C and *E* were cooled in liquid oxygen and *D* in acetone–carbon dioxide. After pumping to a high vacuum, T_5, T_7, and T_9 were closed, T_6 and T_8 being open. The cooling-bath round *E* was removed and the contents allowed to warm slowly to room temperature. T_6 was closed, the bath round *D* removed, and *E* cooled in liquid oxygen. The fractionation was repeated three times. Pure phosphorus trichloride (1·0 ml.) was thus collected in *D*. A sample for analysis was transferred under a high vacuum to a weighed tube attached at J_1. The lower part of the tube containing the sample was then sealed off and finally broken inside the sealed Carius tube (Found : Cl, 77·4. Calc. for PCl_3 : Cl, 77·4%).

Ethylphosphonous Dichloride.—Tetraethyl-lead (twice distilled in nitrogen; b. p. 80°/12 mm.; 1·25 g., 3·9 mmoles) was placed in *F* (Fig. 2). After evacuation, pure phosphorus trichloride (1·0 ml., 11·4 mmoles) was transferred to *F*. Dry nitrogen was admitted to the system through T_{10}, and *F* heated to 110° by an electric heating-coil. The mixture was stirred magnetically for 72 hr. in dry nitrogen. After cooling, the ethylphosphonous dichloride was transferred under a high vacuum to *D*, a small portion being removed under anhydrous conditions as for phosphorus trichloride (above) (Found : Cl, 54·0. Calc. for $C_2H_5Cl_2P$: Cl, 54·1%) (yield, 1·15 ml., 1·5 g., 99%; n_D^{25} 1·4900).

Ethylphosphonic Dichloride.—The distillation vessel (Fig. 3) which contained dry "AnalaR" benzene (5 ml.) was attached by J_4 to J_2. A tube containing sulphuryl chloride (redistilled through a Fenske column; b. p. 68·8°; 1·5 ml.) was attached at J_1. After evacuation, about one-third of the sulphuryl chloride was allowed to evaporate, thus removing volatile impurities, which were collected in the cooled traps *A* and *B*. The pure compound thus obtained (1·0 ml., 1·67 g., 12·3 mmoles) was then transferred to *G*. Ethylphosphonous dichloride (1·15 ml., 1·48 g., 11·0 mmoles) was then transferred in three portions to *G*, the contents of which were allowed to melt slowly after each addition. Benzene and other volatile materials were removed by continous evacuation with a water pump *via* traps *A* and *B*. The liquid in *G* was electrically heated and distilled while the pressure in the system was maintained at 20 mm. Pure ethylphosphonic dichloride (1·35 g., 80%; activity 6 mc) collected in *H*; it had n_D^{20} 1·4670.

Since the b. p. of the phosphonic dichloride (70°/15 mm.) is too high for easy transfer in a high-vacuum system, a specimen for analysis was obtained by using, instead of the tube *H*, an adaptor to which were attached a tube similar to *H* in which the main fraction was collected, and a small weighed tube in which the sample could be collected and sealed off under anhydrous conditions (Found : Cl, 48·2. Calc. for $C_2H_5OCl_2P$: Cl, 48·3%).

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433. *Reactions in Carboxylic Acid–Thionyl Chloride Systems.*

By W. GERRARD and A. M. THRUSH.

The rate of formation of acid chlorides from acids and thionyl chloride depends on the nature of the acid.

In the presence of pyridine, another reaction occurs concurrently with some acids, the acid chloride reacting with unchanged acid to give the anhydride.

RELATIVE merits of different procedures for the preparation of acyl chlorides (R·COCl) have been discussed in several papers (*e.g.*, McMaster and Ahmann, *J. Amer. Chem. Soc.*, 1928, **50**, 145; Clark and Bell, *Trans. Roy. Canad. Soc.*, 1933, **27**, 97; Bauer, *Oil and Soap*, 1946, **23**, 1), but little information has been given from which the probable sequence of reactions can be deduced. From a mixture of acetic acid (1 mol.) and thionyl chloride (1 mol.) at 20°, sulphur dioxide and hydrogen chloride were evolved from the beginning, and reaction was nearly complete after 1 hr.; *iso*butyric acid required 5 and benzoic acid 50 hr. for close approach to the end-point. After 5 days diphenylacetic acid had reacted to the extent of 38%; trichloroacetic acid did not react during 9 days, and even after 12 hr.' heating at 85°, the acid was recovered.

If the mechanism entails the formation of an intermediate chlorosulphinate, R·CO·O·SOCl, which readily decomposes to acyl chloride and sulphur dioxide, the former has but transitory existence.

Carré and Libermann (*Compt. rend.*, 1934, **199**, 1422) observed that pyridine facilitates

formation of trichloroacetyl chloride. We now show that when trichloroacetic acid (1 mol.) and pyridine (1 mol.) are mixed in ether, the pyridinium salt is precipitated. During the addition of thionyl chloride (1 mol.) to this, acyl chloride and probably the salt $C_5H_5N,SO(OH)Cl$ are readily formed. With certain other acids, however, another reaction occurs concurrently; *e.g.*, with acetic, *iso*butyric, *iso*valeric, heptanoic, phenylacetic, diphenylacetic, and benzoic acids the anhydride is formed by the time 0·5 mol. of thionyl chloride has been added (cf. Gerrard and Thrush, *J.*, 1952, 741):

$$\tfrac{1}{2}R{\cdot}CO_2^- {}^+HNC_5H_5 + \tfrac{1}{2}SOCl_2 \longrightarrow \tfrac{1}{2}R{\cdot}COCl + \tfrac{1}{2}C_5H_5N,SO(OH)Cl$$
$$\tfrac{1}{2}R{\cdot}CO_2^- {}^+HNC_5H_5 + \tfrac{1}{2}R{\cdot}COCl \longrightarrow \tfrac{1}{2}(R{\cdot}CO)_2O + \tfrac{1}{2}C_5H_5N,HCl$$

The second reaction has been shown to be rapid at −78°, whereas formation of the acyl chloride–pyridine complex (cf. *Org. Synth.*, 1946, **26**, 1) is very slow, and when formed, the substance does not react very quickly with an acid to give the anhydride. In the systems now described we do not believe that the acid chloride–pyridine complex is a necessary intermediate.

Trichloroacetate anion does not react with trichloroacetyl chloride, but it does so with acetyl chloride; and the acetate anion reacts with trichloroacetyl chloride. However, diphenylacetyl chloride reacts with the diphenylacetate anion to give the anhydride.

If the structure $R{\cdot}CO_2SO{\cdot}$ can be formed at all it should be during the addition of *n*-butyl chlorosulphinate (1 mol.) to the acid (1 mol.) and pyridine (1 mol.) in ether at −10°. The products, however, were in accordance with the formation of the acyl chloride by a mechanism not entailing that structure.

Experimental

Carboxylic Acids and Thionyl Chloride in the Absence of Pyridine.—The acid (1 mol.) and thionyl chloride (1 mol.) were mixed, and the effluent gases trapped by sodium hydroxide in a U-tube attached to the mechanically shaken apparatus kept at 20°. Thionyl chloride alone (blank) gave no significant amount of effluent. Amounts of sulphur dioxide and chloride ion present in the U-tube after different time intervals were determined. The following results are selected from the whole range.

Acetic acid			*iso*Butyric acid.			Benzoic acid		
Time, min.	SO_2, mol.	Cl^-, equiv.	Time, min.	SO_2, mol.	Cl^-, equiv.	Time, hr.	SO_2, mol.	Cl^-, equiv.
3	0·26	0·51	22	0·27	0·43	1·3	0·04	0·08
11	0·56	0·91	73	0·54	0·75	5·9	0·28	0·41
51	0·76	1·12	199	0·71	0·88	30·0	0·76	0·83

Trichloroacetic acid (10·9 g.) and thionyl chloride (7·94 g.) after 9 days at 20° afforded but a trace of effluent. After being at 85° for 12 hr., the acid (10·3 g.), b. p. 95°/12 mm. (Found: Cl, 65·0. Calc.: Cl, 65·1%), and thionyl chloride (6·8 g.), b. p. 75—80°, were recovered.

When diphenylacetic acid (10·6 g.) and thionyl chloride (5·99 g.) were mixed at 20° the evolution of gas was slow; after 5 days the absorption tube contained SO_2, 0·21 mol., and Cl^-, 0·38 equiv. However, when the acid was heated at 85° for 4 hr. with more thionyl chloride (16 g.), diphenylacetyl chloride (10·6 g., 92%), m. p. 55—56° (Found: Cl, 15·4. Calc. for $C_{14}H_{11}OCl$: Cl, 15·4%), was obtained.

Monochloroacetic acid (18·9 g., 1 mol.) and thionyl chloride (23·8 g., 1 mol.) reacted very slowly at 20°; but after being at 90° for 6 hr. the mixture gave the acyl chloride (19·0 g., 86%), b. p. 106—107° (Found: Cl, 62·0. Calc. for $C_2H_2OCl_2$: Cl, 62·8%).

Carboxylic Acid–Thionyl Chloride–Pyridine System.—By the method previously described (*J.*, 1952, 741), dropwise addition of thionyl chloride (0·5 mol.) to a cooled ethereal solution of acid (1 mol.) and pyridine (1 mol.), phenylacetic anhydride (6·1 g., 96%), m. p. 72° (Found: equiv., 127·5. Calc.: equiv., 127·0), was obtained.

When pyridine (1 mol.) was added to a cooled ethereal solution of diphenylacetic acid (1 mol.) the white pyridine salt crystallised (Found: C_5H_5N, 27·1. Calc.: C_5H_5N, 27·1%). Addition of thionyl chloride (2·98 g., 0·5 mol.) to an ethereal suspension of the salt (14·55 g., 1 mol.) afforded diphenylacetic anhydride (9·7 g., 96%), m. p. 96—97° (Found: equiv., 202. Calc.: equiv., 203).

Trichloroacetic acid formed with pyridine a salt insoluble in ether (Found: C_5H_5N, 32·7;

Cl, 42·8. Calc.: C_5H_5N, 32·6; Cl, 43·9%). When thionyl chloride (11·8 g., 0·5 mol.) was added to a cooled suspension of this salt (48·5 g., 1 mol.), and the mixture kept for 12 hr., the ethereal filtrate afforded trichloroacetyl chloride (14·1 g., 0·39 mol.), b. p. 118° [Found: Cl (water-hydrolysable), 19·4. Calc. for C_2OCl_4: Cl (water-hydrolysable), 19·5%], and trichloroacetic acid (5·4 g.), m. p. 58° (Found: Cl, 65·3. Calc. for $C_2HO_2Cl_3$: Cl, 65·1%). Similar results were obtained from the reaction at −78°, and the separated solid was kept in a vacuum until constant in weight (sulphur dioxide having been removed) (33·4 g.) (Found: Cl^-, 0·525 mol., 11·1%; C_5H_5N, 0·94 mol., 44·1%. Calc. for an equimolecular mixture of C_5H_5N,HCl and C_5H_5N,$CCl_3{\cdot}CO_2H$: Cl^-, 9·9; C_5H_5N, 44·2%).

When thionyl chloride (29·7 g., 1 mol.) was added to an ethereal suspension of pyridinium trichloroacetate (60·2 g., 1 mol.) at −10° the solid contained Cl^-, C_5H_5N, and SO_2 in molar ratios 0·96, 0·95, and 0·64, whilst the filtrate afforded trichloroacetyl chloride (42·3 g., 93%), b. p. 117—118° [Found: Cl (water-hydrolysable), 19·5%].

Thionyl chloride (5·9 g., 0·5 mol.), added to an ethereal solution of benzoic acid (12·2 g., 1 mol.) and pyridine (7·9 g., 1 mol.) at −10°, immediately gave a precipitate (Cl^-, 0·96 equiv.; C_5H_5N, 0·96 mol.; SO_2, 0·39 mol.) whilst the filtrate afforded benzoic anhydride (11·0 g., 98%), m. p. 42° (Found: equiv., 113·0. Calc.: equiv., 113·0).

Reactions in which thionyl bromide was used instead of thionyl chloride gave similar results. Yields of anhydride obtained were: acetic, 94%; *n*-heptanoic, 95%; benzoic, 99%.

n-Butyl Chlorosulphinate–Carboxylic Acid–Pyridine.—The chlorosulphinate (15·65 g., 1 mol.) was used instead of thionyl chloride. Added to a well-shaken ethereal solution of acetic acid (6·0 g., 1 mol.) and pyridine (7·9 g., 1 mol.) at −10°, it immediately afforded a precipitate (Cl^-, 0·97 equiv.; C_5H_5N, 0·94 mol.; SO_2, 0·44 mol.), acetic anhydride (4·71 g., 0·46 mol.), b. p. 136—138°, $n_D^{18\cdot5}$ 1·3930 (Found: equiv., 51·7. Calc.: equiv., 51·0), and di-*n*-butyl sulphite (9·7 g., 0·50 mol.), b. p. 109—110°/15 mm., n_D^{18} 1·4325. Similarly, the chlorosulphinate (20 g., 1 mol.), *n*-heptanoic acid (16·6 g.), and pyridine (10·1 g.) gave a precipitate (Cl^-, 0·97 equiv.; C_5H_5N, 0·97 mol.; SO_2, 0·3 mol.), di-*n*-butyl sulphite (12·9 g., 0·5 mol.), b. p. 104°/11 mm., n_D^{20} 1·4318 (Found: S, 16·3. Calc. for $C_8H_{18}O_3S$: S, 16·4%), and *n*-heptanoic anhydride (14·8 g., 0·48 mol.), b. p. 106—108°/0·2 mm., n_D^{20} 1·4330 (Found: equiv., 121·0. Calc.: equiv., 121·0). The chlorosulphinate (15·65 g., 1 mol.), benzoic acid (12·2 g.), and pyridine (7·9 g.) afforded a precipitate (Cl^-, 0·898 equiv.; C_5H_5N, 0·880 mol.; SO_2, 0·014 mol.), impure di-*n*-butyl sulphite (7·4 g.), b. p. 70—80°/0·05 mm. (Found: S, 14·7%), benzoic anhydride (7·9 g.), b. p. 135—140°/0·05 mm. (Found: equiv., 113·4. Calc.: equiv., 113·0), and a black residue (3·0 g.).

Acyl Chloride–Carboxylic Acid–Pyridine.—Addition of *n*-heptanoyl chloride (8·49 g., 1 mol.) to an ethereal solution of *n*-heptanoic acid (7·43 g., 1 mol.) and pyridine (4·52 g., 1 mol.) at −10° immediately afforded pyridine hydrochloride (6·3 g., 96%) (Found: Cl, 30·7; C_5H_5N, 68·0. Calc. for C_5H_5N,HCl: Cl, 30·7; C_5H_5N, 68·4%). The filtrate afforded *n*-heptanoic anhydride (13·4 g., 97%), b. p. 112—114°/0·3 mm., d_0^{18} 0·9240, n_D^{20} 1·4321 (Found: equiv., 120·8. Calc.: equiv., 121·0). This reaction was shown to be almost instantaneous at −78°. Addition of the acid to a cooled ethereal solution of the acid chloride and pyridine readily gave the anhydride in 95% yield. To form the complex, pyridine (7·9 g., 1 mol.) was added to an ethereal solution of *n*-heptanoyl chloride (14·86 g., 1 mol.). No immediate precipitation occurred, but the *n*-heptanoyl chloride–pyridine complex (11·4 g., 50% after 3 days) separated slowly (Found: Cl, 16·3; C_5H_5N, 34·1. Calc. for $C_{12}H_{18}ONCl$: Cl, 15·6; C_5H_5N, 34·7%). Addition of *n*-heptanoic acid (4·52 g., 1 mol.) to an ethereal suspension of this complex (7·92 g., 1 mol.) at −10° afforded, after 15 min., impure pyridine hydrochloride (3·77 g., 94%) (Found: Cl, 28·7; C_5H_5N, 60·9%) and *n*-heptanoic anhydride (7·1 g., 84%), b. p. 110—115°/0·5 mm., n_D^{20} 1·4326 (Found: equiv., 122·0. Calc.: equiv., 121·0). It was shown that trichloroacetyl chloride did not react with an ethereal suspension (or chloroform solution) of pyridinium trichloroacetate even on prolonged shaking at room temperature. However, acetyl chloride (3·93 g., 1 mol.) when shaken with an ethereal suspension of pyridinium trichloroacetate for 20 hr. afforded acetic trichloroacetic anhydride (1·5 g., 14·6%), b. p. 90—92°/14 mm., n_D^{18} 1·4580 (Found: equiv., 105; Cl, 52·0. Calc.: equiv., 103; Cl, 51·8%).

Trichloroacetyl chloride (9·1 g., 1 mol.) when added dropwise to an ethereal solution of acetic acid (3·0 g., 1 mol.) and pyridine (3·95 g., 1 mol.) at −10° afforded a precipitate (8·95 g.) of an equimolecular mixture of pyridinium trichloroacetate and pyridine hydrochloride (Found: Cl^-, 9·8; C_5H_5N, 43·7. Calc.: Cl^-, 9·9; C_5H_5N, 44·1%) and an inseparable mixture of trichloroacetyl chloride and acetic anhydride. Addition of trichloroacetyl chloride (4·55 g., 0·5 mol.) to the same quantities of acetic acid and pyridine afforded a precipitate (8·4 g.) with

the same composition as before and acetic anhydride (2·5 g., 93%), b. p. 138°, n_D^{20} 1·3992 (Found: equiv., 52·0. Calc.: equiv., 51·0).

Dropwise addition of trichloroacetyl chloride (9·1 g., 1 mol.) to an ethereal solution of *n*-butyl alcohol (3·7 g., 1 mol.) and pyridine (3·95 g., 1 mol.) afforded an immediate precipitate of impure pyridine hydrochloride (5·79 g., 101%) (Found: Cl, 29·1%), and the filtrate afforded *n*-butyl trichloroacetate (9·8 g., 90%), b. p. 84°/10 mm., n_D^{20} 1·4530, d_4^{20} 1·276 (Found: Cl, 48·2. Calc. for $C_6H_9O_2Cl_3$: Cl, 48·5%). When pyridine (2·42 g., 1 mol.) was added to a solution of trichloroacetyl chloride (5·58 g., 1 mol.) in light petroleum no precipitate separated even on long standing, and after the unchanged reactants had been removed at 40°/20 mm. only a small residue (0·1 g.) remained.

Dropwise addition of diphenylacetyl chloride (4·1 g., 1 mol.) to an ethereal suspension of pyridinium diphenylacetate at −10° afforded pyridine hydrochloride (1·93 g., 93%) and diphenylacetic anhydride (7·15 g., 98%), m. p. 96—97° (Found: equiv., 202·0. Calc.: equiv., 203·0).

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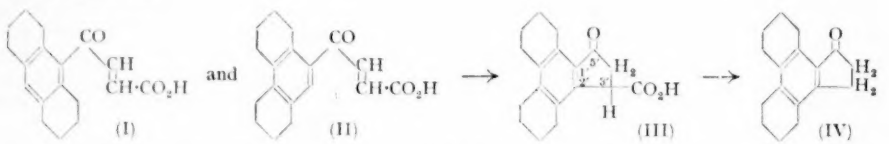
434. *Preparation and Isomerisation of Aromatic Ketones and Keto-acids.*

By G. BADDELEY and R. WILLIAMSON.

The following changes have been effected through the agency of excess of aluminium chloride: β-(*s*-octahydro-9-anthroyl)- and β-(*s*-octahydro-9-phenanthroyl)-acrylic acids * to 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-5′-keto-9 : 10-*cyclo*pentenophenanthrene-3′-carboxylic acid (I and II ⟶ III); 9-acetyl-*s*-octahydroanthracene to 7-acetyl-2-methyl-4 : 5-*cyclo*hexenoindane (VI) and 7-acetyl-3-methyl-4 : 5-*cyclo*hexenoindene (VII); 1-keto-*s*-dodecahydrotriphenylene * (IX) to 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-1-keto-4′-methyl-9 : 10-*cyclo*pentenophenanthrene (X) and 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-8-keto-3′-methyl-9 : 10-*cyclo*penta-1′ : 3′-dienophenanthrene (XI).

The 10-acetyl derivatives of *s*-octahydro-9-methyl- and 9-ethyl-*s*-octahydro-anthracene undergo intermolecular migration of acetyl or alkyl groups.

SUCCINOYLATION of *s*-octahydroanthracene * by the Friedel–Crafts method is reported to afford a mixture of β-(*s*-octahydro-9-anthroyl)- and β-(*s*-octahydro-9-phenanthroyl)-propionic acids (Badger, Carruthers, and Cook, *J.*, 1949, 2044); the latter is provided by isomerisation of the former (see Experimental), a process requiring the presence of undissolved aluminium chloride or the chloride in excess (*J.*, 1950, 944). This condition obtains almost invariably when powdered aluminium chloride is added to a mixture of the other two reactants or when the solvent is carbon disulphide, and can readily be avoided when methylene or ethylene chloride is the solvent (*J.*, 1952, 3289, 3605); thus only β-(*s*-octahydro-9-anthroyl)propionic acid is obtained when a solution of succinic anhydride in ethylene chloride is saturated with aluminium chloride and decanted into *s*-octahydroanthracene; reaction is complete in a few minutes. If, at this stage, aluminium chloride is added and the mixture is kept for several days, the corresponding phenanthroylpropionic acid is obtained.

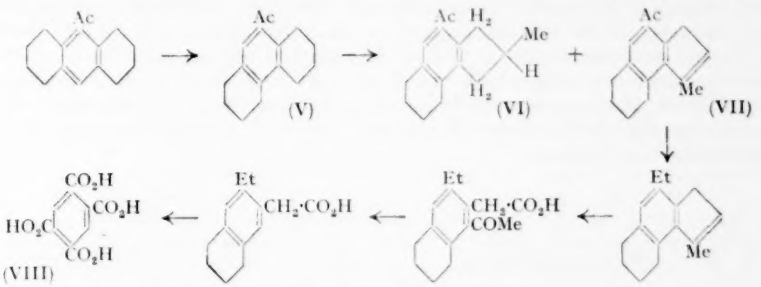


(I) (II) (III) (IV)

Reaction of maleic anhydride with *s*-octahydro-anthracene and -phenanthrene in the absence of excess of aluminium chloride or undissolved chloride readily affords β-(*s*-octahydro-9-anthroyl)- and β-(*s*-octahydro-9-phenanthroyl)-acrylic acid (I and II) respectively; in

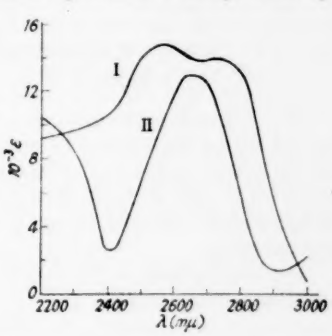
* In this paper *s*-octahydro and *s*-dodecahydro are used when the central ring is aromatic.

each instance excess of reagent effects isomerisation with formation of 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-5′-keto-9 : 10-*cyclo*pentenophenanthrene-3′-carboxylic acid (III). This acid is obtained in 90% yield when each of the acrylic acids is fused with excess of aluminium chloride at 100°, and in 50% yield when concentrated sulphuric acid is used. It was identified by decarboxylation to (IV) which has been described by Badger, Carruthers,



Cook, and Schoental (*J.*, 1949, 169). Cyclisation of β-aroylacrylic acids was reported first by Lambert and Martin (*Bull. Soc. chim. Belg.*, 1952, **61**, 132) and one of us (G. B.) was unaware of this when submitting papers (*J.*, 1952, 3289, 3605).

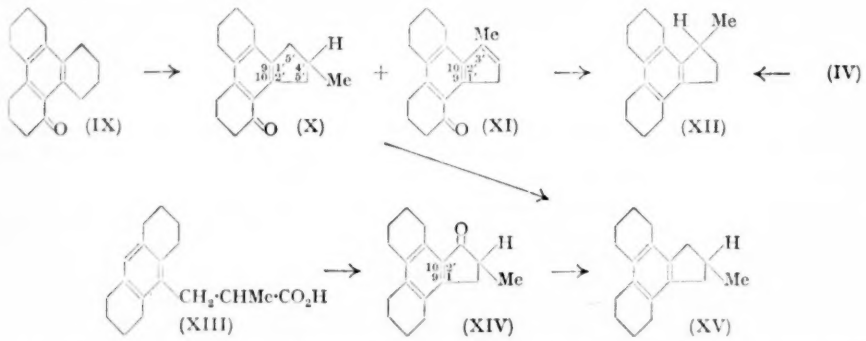
Acetylation of *s*-octahydro-anthracene and -phenanthrene, while affording the 9-acetyl derivatives when *excess* of aluminium chloride is absent, provides 7-acetyl-2-methyl-4 : 5-*cyclo*hexenoindane (VI) when the reaction mixtures are kept for several days in the presence of excess of reagent. This ring contraction, which is not a feature of reaction of these hydrocarbons with succinic or maleic anhydride, was observed previously on fusion with aluminium chloride at 100° (Baddeley and Pendleton, *J.*, 1952, 807), the indane being contaminated by an oil representing 25% of the product. The oil has now been examined and is probably a mixture of (VI) (3 parts) and 7-acetyl-3-methyl-4 : 5-*cyclo*hexenoindene (VII) (1 part) : it was reduced by the Clemmensen method to a hydrocarbon which was ozonised; the product, like the original oil and the hydrocarbon obtained from it by Clemmensen reduction, absorbed hydrogen (0·25 mol.) on catalytic hydrogenation; subsequent oxidation with alkaline hydrogen peroxide provided a keto-acid which was separated from saturated hydrocarbon; the keto-acid gave a positive iodoform test and was hydrolysed by syrupy phosphoric acid to acetic acid and an aromatic acid which afforded benzene-1 : 2 : 4 : 5-tetracarboxylic acid when oxidised by dilute nitric acid. These results are compatible with the formulation (VII ⟶ VIII). The hydrocarbon recovered after ozonolysis is 7-ethyl-2-methyl-4 : 5-*cyclo*hexenoindane and like an authentic sample, obtained by Clemmensen reduction of (VI), afforded 7-ethyl-2-methyl-4 : 5-benzindane on catalytic dehydrogenation.



1-Keto-*s*-dodecahydrotriphenylene (IX) also affords two products when fused with aluminium chloride at 100°. Chromatography on alumina gave a ketone $C_{18}H_{22}O$, as the more mobile component. This afforded 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-4′-methyl-9 : 10-*cyclo*pentenophenanthrene (XV) when reduced by the Clemmensen method and is 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-1-keto-4′-methyl-9 : 10-*cyclo*pentenophenanthrene (X). Its ultra-violet absorption spectrum (see Figure, curve II) is similar to that of acetophenone. The other component is a ketone $C_{18}H_{20}O$, and is probably 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-8-keto-3′-methyl-9 : 10-*cyclo*penta-1′ : 3′-dienophenanthrene (XI) for the following reasons: (i) Catalytic hydrogenation provided a dihydro-derivative which gave 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-3′-methyl-9 : 10-*cyclo*pentenophenanthrene (XII) by Clemmensen reduction.

(ii) Its ultra-violet absorption spectrum has a broad band (see Figure, curve I), probably formed by overlap of two bands, and is compatible with conjugation of a carbonyl group and an ethylenic linkage with a benzene ring but not with one another. (iii) The change (IX ⟶ X + XI) is analogous to (V ⟶ VI + VII).

Authentic samples of (XII) and (XV) were needed for comparison; the former was prepared from (IV) by standard procedure and the latter as follows: Interaction of 9-chloromethyl-*s*-octahydroanthracene and sodiomethylmalonic ester and subsequent hydrolysis and decarboxylation at 200° gave α-methyl-β-(9-*s*-octahydroanthryl)propionic acid (XIII), which was isomerised and cyclised to 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-3′-keto-4′-methyl-9 : 10-*cyclo*pentenophenanthrene (XIV) by the action of anhydrous hydrogen fluoride (see Badger, Carruthers, Cook, and Schoental, *J.*, 1949, 169); this ketone gave (XV) on Clemmensen reduction.



The 10-acetyl derivatives of *s*-octahydro-9-methyl- and 9-ethyl-*s*-octahydro-anthracene did not afford derivatives of hydrindacene on fusion with aluminium chloride; instead, intermolecular migration of acetyl and/or alkyl groups occurred. The former gave a mixture containing the 9-methyl derivatives of *s*-octahydroanthracene and *s*-octahydrophenanthrene, and the latter, a mixture containing 9-ethyl- and 9-acetyl-*s*-octahydrophenanthrene.

The mechanisms of the reactions effected by aluminium chloride will be discussed in a further communication.

Experimental

Materials.—Hydrocarbons. (i) *s*-Octahydro-9-methylanthracene was obtained by catalytic reduction of the 9-chloromethyl derivative (Badger, Carruthers, and Cook, *loc. cit.*). During chloromethylation of *s*-octahydroanthracene by paraformaldehyde and hydrogen chloride in glacial acetic acid, sufficient solvent to prevent separation of an oil must be used, otherwise considerable quantities of the 9 : 10-bischloromethyl derivative are obtained.

(ii) 9-Ethyl-*s*-octahydroanthracene was obtained from the 9-acetyl derivative by a three-stage process: The ketone (23 g.) was reduced by lithium aluminium hydride (1·2 g.) in ethereal solution to *s-octahydro-9-1′-hydroxyethylanthracene* (19 g.), b. p. 170°/0·25 mm., plates (from ethanol), m. p. 104° (Found: C, 83·7; H, 10·0. $C_{16}H_{22}O$ requires C, 83·5; H, 9·7%), and afforded the 9-vinyl derivative (18 g.), b. p. 154°/0·5 mm. (Found: C, 90·5; H, 9·1. $C_{16}H_{20}$ requires C, 90·6; H, 9·4%), when distilled from a trace of sulphuric acid. Catalytic hydrogenation then provided the required hydrocarbon.

(iii) Finely powdered *s*-octahydro-1′-keto-9 : 10-*cyclo*pentenophenanthrene (2 g.) was gradually added to a stirred solution of magnesium (0·3 g.) in methyl iodide (1·5 g.) and ether (50 c.c.); the mixture was kept overnight and, when decomposed with ammonium chloride solution, afforded the tertiary *alcohol*; this crystallised from ethanol in plates, m. p. 135—137° (Found: C, 84·1; H, 9·8. $C_{18}H_{24}O$ requires C, 84·4; H, 9·4%). It was dissolved in a minimum of benzene and vigorously stirred with formic acid (90%; 10 c.c.) for 4 hr. After addition of water, the benzene layer was separated and washed with water; removal of solvent provided a residue which was hydrogenated in ethanol over Raney nickel. The resultant

1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-*octahydro*-3′-*methyl*-9 : 10-cyclo*pentenophenanthrene* (XII) crystallised from aqueous acetic acid in needles, m. p. 115° (Found : C, 89·6; H, 9·9. $C_{18}H_{24}$ requires C, 90·0; H, 10·0%).

(iv) 9-Chloromethyl-*s*-octahydroanthracene (23 g.) was added to a solution of sodium (2·3 g.) in methylmalonic ester (17·4 g.) and toluene (75 c.c.); the mixture was kept overnight and was then refluxed for 7 hr. After addition of water, the organic layer was separated, toluene was removed by distillation, and the residue was refluxed for 4 hr. with 30% sodium hydroxide solution. Insoluble material was extracted by chloroform, and the aqueous solution was acidified; the precipitated dicarboxylic acid (m. p. 190°) was decarboxylated at 200° and the product recrystallised from aqueous acetic acid (charcoal); *α-methyl-β-(s-octahydro-9-anthryl)-propionic acid* (15 g.) separated in needles, m. p. 151—152° (Found : C, 79·2; H, 8·7%; equiv., 280. $C_{18}H_{14}O_2$ requires C, 79·5; H, 8·8%; equiv., 272). This acid (10 g.) in anhydrous hydrofluoric acid (120 c.c.) was set aside for 60 hr. and afforded 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-*octahydro*-3′-*keto*-4′-*methyl*-9 : 10-cyclo*pentenophenanthrene* (XIV) (5 g.), needles (from aqueous acetic acid), m. p. 158—160° (Found : C, 85·0; H, 8·6. $C_{18}H_{22}O$ requires C, 85·0; H, 8·7%). This ketone (3 g.) was reduced by the Clemmensen method to 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-*octahydro*-4′-*methyl*-9 : 10-cyclo*pentenophenanthrene* (XV) (2·8 g.), needles (from aqueous acetic acid), m. p. 135° (Found : C, 89·6; H, 9·7. $C_{18}H_{24}$ requires C, 90·0; H, 10·0%).

(v) Reduction of 7-acetyl-2-methyl-4 : 5-*cyclo*hexenoindane (Baddeley and Pendleton, *loc. cit.*) by the Clemmensen method provided the 7-ethyl-2-methyl derivative which gave 7-ethyl-2-methyl-4 : 5-benzindane by dehydrogenation; the *picrate* crystallised from ethanol in brick-red needles, m. p. 120—121° (Found : C, 60·5; H, 5·0; N, 10·0. $C_{22}H_{21}O_7N_3$ requires C, 60·2; H, 4·8; N, 9·6%).

Ketones. Acetyl chloride (1·1 mols.) was added to a suspension of aluminium chloride (1·3 mols.) in methylene or ethylene chloride, and the solution was slowly decanted from undissolved aluminium chloride into a solution of aromatic hydrocarbon (1 mol.) in methylene or ethylene chloride. Reaction was complete after a few minutes and the product was worked up in the usual way. 9-Acetyl-*s*-octahydroanthracene crystallised from methanol in large needles, m. p. 71° (Arnold and Barnes, *J. Amer. Chem. Soc.*, 1944, **66**, 963). 10-*Acetyl*-*s*-*octahydro*-9-*methylanthracene* crystallised from ethanol in needles, m. p. 124° (Found : C, 84·3; H, 8·9. $C_{17}H_{22}O$ requires C, 84·3; H, 9·1%), and 10-*acetyl*-9-*ethyl*-*s*-*octahydroanthracene*, b. p. 166°/0·2 mm., in needles, m. p. 136° (Found : C, 83·9; H, 9·6. $C_{18}H_{24}O$ requires C, 84·4; H, 9·4%). *s*-Dodecahydro-1-ketotriphenylene (IX), m. p. 221°, was obtained by the action of anhydrous hydrofluoric acid on γ-(*s*-octahydro-9-phenanthryl)butyric acid (Badger, Carruthers, and Cook, *loc. cit.*).

Succinic Anhydride and s-*Octahydroanthracene in Ethylene Chloride.*—(i) A mixture of the anhydride (12 g., 1·2 mols.) and aluminium chloride (30 g., 2·2 mols.) in solvent (100 c.c.) was stirred for 15 min. and the solution was decanted from undissolved chloride into a solution of the hydrocarbon (18·6 g.) in solvent (100 c.c.). After 10 min., the mixture was decomposed with ice and hydrochloric acid and afforded β-(*s*-octahydro-9-anthroyl)propionic acid (15 g.), m. p. and mixed m. p. 214°, as the only product which was not volatile in steam.

(ii) When aluminium chloride (45 g., 3 mols.) was used and the mixture kept for 3 days at 18°, β-(*s*-octahydro-9-phenanthroyl)propionic acid (18 g.), m. p. and mixed m. p. 148°, was obtained.

(iii) A mixture of β-(*s*-octahydro-9-anthroyl)propionic acid (5·7 g.) and aluminium chloride (10 g., 4 mols.) in solvent (50 c.c.) was kept for 2 days at 18° and afforded β-(*s*-octahydro-9-phenanthroyl)propionic acid (4 g.). This acid (17 g.) was obtained from a mixture of succinic anhydride (10 g.), aluminium chloride (30 g.), *s*-octahydrophenanthrene (16 g.), and solvent (200 c.c.) which had been kept for 10 min.

Maleic Anhydride and s-*Octahydroanthracene in Ethylene Chloride.*—(i) A mixture of the anhydride (2·5 g., 1 mol.) and aluminium chloride (10 g., 2·5 mols.) in solvent (50 c.c.) was stirred for 15 min. and the clear solution was decanted into the hydrocarbon (4·7 g.) in solvent (50 c.c.). After several min. the mixture was decomposed in the usual way and afforded 2-(*s*-*octahydro*-9-*anthroyl*)*acrylic acid* (I) (6·5 g.) as bright yellow needles, m. p. 208° (from glacial acetic acid) (Found : C, 75·6; H, 7·0%; equiv., 287. $C_{18}H_{20}O_3$ requires C, 76·0; H, 7·0%; equiv., 284). It afforded the corresponding propionic acid on hydrogenation.

When subjected to the above process, *s*-octahydrophenanthrene (4·7 g.) afforded 2-(*s*-*octahydro*-9-*phenanthroyl*)*acrylic acid* (II) (6 g.) which crystallised from glacial acetic acid in yellow needles, m. p. 175—177° (Found : C, 76·4; H, 7·2%), and provided the corresponding propionic acid on hydrogenation.

(ii) When excess of aluminium chloride was used in the above reactions and the mixtures kept for several days, *s*-octahydro-anthracene and -phenanthrene afforded the same acid, m. p. 237° (decomp.) [*methyl* ester, m. p. and mixed m. p. 138° (Found : C, 76·8; H, 7·6. $C_{19}H_{22}O_3$ requires C, 76·5; H, 7·4%)]. This acid 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-5′-keto-9 : 10-*cyclo*pentenophenanthrene-3′-carboxylic acid (III) was obtained in 90% yield when the above acrylic acids were added to aluminium chloride–sodium chloride at 100° and in 50% yield by the action of sulphuric acid at 100°. The acid (9·7 g.) was decarboxylated by copper chromite (2 g.) in quinoline (40 c.c.) at 200°; the product provided colourless needles (6 g.), m. p. 196° when sublimed at 190°/0·1 mm. and these formed a 2 : 4-dinitrophenylhydrazone, m. p. 295° (Badger, Carruthers, and Cook, *loc. cit.*, record the m. p. of 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-3′-keto*cyclo*pentenophenanthrene and of its 2 : 4-dinitrophenylhydrazone as 197—198° and 298° respectively). Clemmensen reduction of this ketone gave 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-*octahydro*-9 : 10-cyclo*pentenophenanthrene* which crystallised from ethanol in colourless needles, m. p. 153° (Found : C, 89·7; H, 9·9. $C_{17}H_{22}$ requires C, 90·2; H, 9·8%).

Acetyl Chloride and s-Octahydroanthracene in Ethylene Chloride.—(i) A solution obtained from acetyl chloride (8·5 g.) and aluminium chloride (18 g.) in solvent (100 c.c.) was decanted from undissolved aluminium chloride into a solution of the hydrocarbon (18·6 g.) in solvent (100 c.c.); the mixture was decomposed after 5 min. at room temperature and afforded 9-acetyl-*s*-octahydroanthracene (17 g.), b. p. 175°/0·7 mm., m. p. and mixed m. p. 72°.

(ii) The reaction mixture was prepared as in the previous experiment, and excess of aluminium chloride (14 g., 1 mol.) was then added. After 2 days, at room temperature, decomposition afforded 7-acetyl-2-methyl-4 : 5-*cyclo*hexenoindane (VI) (17 g.), b. p. 148°/0·1 mm., m. p. and mixed m. p. 98°.

Aromatic Ketones and Aluminium Chloride.—(i) 10-*Acetyl-s-octahydro*-9-*methylanthracene*. This ketone (5 g.), aluminium chloride (8 g., 3 mols.), and sodium chloride (0·5 g.) were heated together at 100° for 3 hr. After decomposition with ice and hydrochloric acid, the product (4·4 g.), b. p. 135—200°/0·5 mm., was dissolved in light petroleum and extracted with sulphuric acid (90%). The petroleum retained aromatic hydrocarbon (1·0 g.) and this was dehydrogenated over palladised charcoal (5%) at 260°; the product was crystallised from ethanol and afforded colourless needles of 9-methylphenanthrene, m. p. and mixed m. p. 90° (Found : C, 93·3; H, 6·4. Calc. for $C_{15}H_{12}$: C, 93·7; H, 6·3%). The filtrate was fluorescent and addition of an ethanolic solution of picric acid precipitated 9-methylanthracene picrate in deep red needles (from benzene), m. p. and mixed m. p. 137° (Found : C, 59·6; H, 3·6; N, 9·9. Calc. for $C_{21}H_{15}O_7N_3$: C, 59·8; H, 3·6; N, 10·0%). Ketonic products, isolated by dilution of the acid extract, distilled over a wide range of temperature and were not investigated.

(ii) 10-*Acetyl*-9-*ethyl*-*s*-*octahydroanthracene*. This ketone (10 g.), aluminium chloride (15 g.), and sodium chloride (1·5 g.) were heated together at 100° for 3 hr. Recovered organic material afforded a pale yellow oil (6·5 g.), b. p. 140—180°/0·1 mm. Separation by sulphuric acid as in the previous experiment gave mainly ketonic material, b. p. 170—180°/0·1 mm., which was 9-acetyl-*s*-octahydrophenanthrene (V) since oxidation with selenium dioxide and then alkaline hydrogen peroxide (Arnold and Rondestvedt, *J. Amer. Chem. Soc.*, 1945, **67**, 1265) afforded *s*-octahydro-9-phenanthroic acid, m. p. and mixed m. p. 241°. The material which did not dissolve in sulphuric acid contained 9-ethyl-*s*-octahydrophenanthrene; when dehydrogenated with palladised charcoal at 260° it afforded 9-ethylphenanthrene which was identified by its picrate, m. p. and mixed m. p. 124° (Pschorr, *Ber.*, 1906, **39**, 3128) (Found : C, 60·1; H, 3·8. Calc. for $C_{22}H_{17}O_7N_3$: C, 60·7% H, 3·9%)

(iii) 9-*Acetyl*-*s*-*octahydroanthracene*. A mixture of this ketone (50 g.), aluminium chloride (76 g.), and sodium chloride (3 g.) was heated at 100° for 2 hr. Decomposition gave a semi-solid product (45 g.), b. p. 148°/0·12 mm., consisting of solid, 7-acetyl-2-methyl-4 : 5-*cyclo*hexenoindane (VI) (30 g.), m. p. and mixed m. p. 98°, and oil (15 g.). (Very little oil was formed when the ketone was isomerised in ethylene chloride at room temperature, but oil was gradually formed when 7-acetyl-2-methyl-4 : 5-*cyclo*hexenoindane was fused with excess of aluminium chloride at 100°.) The oil (Found : C, 84·5; H, 9·4. Calc. for $C_{16}H_{20}O$: C, 84·2; H, 8·8%) contained unsaturated material since it decolorised bromine in carbon tetrachloride and aqueous permanganate, and absorbed hydrogen (0·25 mol.) over palladised charcoal (5%). Oxidation by Arnold and Rondestvedt's method (*loc. cit.*) provided a mixture of carboxylic acids (Found: C, 78·2; H, 7·9%; equiv., 227. Calc. for $C_{15}H_{18}O_2$: C, 78·3; H, 7·8%; equiv., 230). Neither the oil nor the mixture of acids obtained from it could be separated into their components. The oil (15 g.) afforded hydrocarbon (11 g.), b. p. 130—135°/0·2 mm., on Clemmensen reduction; the hydrocarbon absorbed hydrogen (0·25 mol.) on catalytic hydrogen-

ation. The hydrocarbon (10·0 g.) in ethyl acetate was subjected to a stream of ozonised oxygen for 2 hr.; the product, over palladised charcoal (30%), absorbed hydrogen (270 c.c.); this volume is compatible with the view that the hydrocarbon contains 25% of indene. After removal of solvent, the residue, in ethanol (10 c.c.), was treated with hydrogen peroxide (30%; 5 c.c.) and sodium hydroxide solution (10%) until there was no further reaction; after being heated at 80° for 30 min., the mixture was cooled, diluted with water, and extracted with ether. The ethereal layer contained 7-ethyl-2-methyl-4 : 5-*cyclo*hexenoindane, b. p. 135°/0·2 mm. A sample (1 g.) was dehydrogenated over palladised charcoal at 260° and afforded 7-ethyl-2-methyl-4 : 5-benzindane. Its picrate crystallised from ethanol in brick-red needles, m. p. and mixed m. p. 120—121° (Found : C, 60·5; H, 5·0; N, 10·0. Calc. for $C_{22}H_{21}O_7N_3$: C, 60·2; H, 4·8; N, 9·6%). On acidification, the aqueous layer provided a keto-acid which gave a ready iodoform reaction; it evolved acetic acid when heated with syrupy phosphoric acid at 180° and the residue, which was isolated by dilution with water and extraction with chloroform, afforded benzene-1 : 2 : 4 : 5-tetracarboxylic acid (tetramethyl ester, m. p. and mixed m. p. 124°) when heated with nitric acid (*d* 1·1) at 160° for 3 hr.

(iv) s-*Dodecahydro-1-ketotriphenylene*. This ketone (5 g.), aluminium chloride (15 g.), and sodium chloride (5 g.) were fused together at 100° for 1 hr. After decomposition with ice and hydrochloric acid the product (3·8 g.), b. p. 210°/0·5 mm., gradually crystallised. Chromatography in light petroleum on activated grade "H" alumina provided two components : 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-*octahydro-1-keto-4′-methyl*-9 : 10-cyclo*pentenophenanthrene* (X), the more mobile, crystallised from ethanol in needles, m. p. 148—149° (Found : C, 85·1; H, 8·9. $C_{18}H_{22}O$ requires C, 85·05; H, 8·7%); 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-*octahydro-8-keto-3′-methyl*-9 : 10-cyclo*penta*-1′ : 3′-*dienophenanthrene* (XI), the other component, crystallised from ethanol in long needles, m. p. 116—117° (Found : C, 85·1; H, 7·9. $C_{18}H_{20}O$ requires C, 85·6; H, 7·9%). Reduction of (X) by the Clemmensen method provided 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-4′-methyl-9 : 10-*cyclo*pentenophenanthrene, m. p. and mixed m. p. 135° (Found : C, 89·6; H, 9·7. Calc. for $C_{18}H_{24}$: C, 90·0; H, 10·0%) after recrystallisation from aqueous acetic acid. The compound (XI) decolorised bromine in carbon tetrachloride and aqueous permanganate and absorbed hydrogen (1 mol.) over Raney nickel; the cyclo*penteno*-derivative crystallised from ethanol in needles, m. p. 145° (Found : C, 85·4; H, 8·9. $C_{18}H_{22}O$ requires C, 85·0; H, 8·7%), readily formed a 2 : 4-dinitrophenylhydrazone, depressed the m. p. of (X) on admixture, and afforded 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-3′-methyl-9 : 10-*cyclo*pentenophenanthrene, m. p. and mixed m. p. 115° (Found : C, 89·5; H, 9·9. Calc. for $C_{18}H_{24}$: C, 90·0; H, 10·0%), on Clemmensen reduction.

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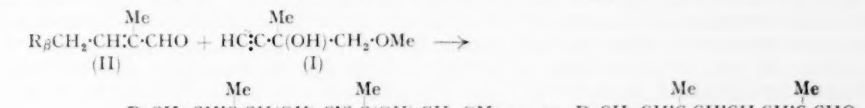
435. *Studies in the Polyene Series. Part XLIX.* Acetylenic Alcohols from Methoxyacetone, and their Conversion into Unsaturated Aldehydes.*

By RASHID AHMAD and B. C. L. WEEDON.

A modification of the Inhoffen method has been used to prepare a number of αβ-unsaturated α-methyl-aldehydes.

A NEW method for the preparation of αβ-unsaturated α-methyl-aldehydes, valuable intermediates for polyene syntheses, was developed by Inhoffen and his collaborators who condensed 1-methoxy-2-methylbut-3-yn-2-ol (I) with the C_{14} aldehyde (II) to obtain a



Rβ = 2 : 6 : 6-trimethyl*cyclo*hexenyl.

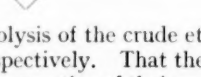
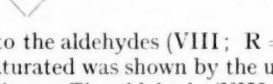
glycol (III) which, by anionotropic rearrangement, semihydrogenation of the triple bond, and dehydration, was converted into the C_{19} aldehyde (IV) (Inhoffen, Bohlmann, Bartram,

* Part XLVIII, *J.*, 1953, 1584.

Rummert, and Pommer, *Annalen*, 1950, **570**, 54; Inhoffen and Leibner, *ibid.*, 1951, **575**, 105). A similar route has now been used for the preparation of other unsaturated aldehydes from typical, monosubstituted, acetylenes.

Reaction of methoxyacetone with the Grignard complexes of hex-1-yne, phenylacetylene, and 1-ethynyl*cyclo*hexene gave the acetylenic alcohols (V; R = Bu^n, Ph, and *cyclo*hexenyl) (*ca.* 70%). Partial reduction of the triple bond was accomplished, in good yield, either by catalytic hydrogenation (V; R = Bu^n and Ph), or by treatment with lithium aluminium hydride (V; R = Ph and *cyclo*hexenyl) (cf. Chanley and Sobotka, *J. Amer. Chem. Soc.*, 1949, **71**, 4140). Dehydration of the resulting ethylenic alcohols (VI), and

$$\underset{\text{(V)}}{RC{:}C{\cdot}C(Me)(OH){\cdot}CH_2{\cdot}OMe} \longrightarrow \underset{\text{(VI)}}{RCH{:}CH{\cdot}C(Me)(OH){\cdot}CH_2{\cdot}OMe} \longrightarrow \underset{\text{(VII)}}{RCH{:}CH{\cdot}C(Me){:}CH{\cdot}OMe} \longrightarrow \underset{\text{(VIII)}}{RCH_2{\cdot}CH{:}C(Me){\cdot}CHO}$$

(IX)  (X) 

subsequent hydrolysis of the crude ethers (VII), led to the aldehydes (VIII; R = Bu^n and Ph) and (IX), respectively. That these were αβ-unsaturated was shown by the ultra-violet light absorption properties of their crystalline derivatives. The aldehyde (VIII; R = Ph) has been prepared previously by a Darzens reaction with benzylideneacetone (Linnell and Shen, *J. Pharm. Pharmacol.*, 1949, **1**, 971); the m. p.s of the derivatives of the two specimens are in good agreement.

The spectrum (see Table) of the *cyclo*hexylidenealdehyde exhibited, in addition to the maxima characteristic of a conjugated diene-aldehyde, a band of low intensity at 2270 Å. This suggests that the product (IX) also contained some (*ca.* 20%) of the isomeric *cyclo*hexenyl-aldehyde (X), a lower homologue of the C_{14} aldehyde (II) [cf. equilibrium between *cyclo*hexylidene- and *cyclo*hexenyl-acetaldehyde (Aldersley and Burkhardt, *J.*, 1938, **545**; *cf.* Dimroth, *Ber.*, 1938, **71**, 1333), and the corresponding acetone derivatives (Kon, *Ann. Reports*, 1932, **29**, 138)].

Finally, the new aldehyde synthesis was applied to the diacetylenic glycol (XI), formed in 70% yield by the oxidative coupling of the alcohol (I). Reduction of (XI) with lithium aluminium hydride (cf. Ahmad, Sondheimer, Weedon, and Woods, *J.*, 1952, 4089) gave the diene glycol (XII), as a crystalline solid in 80% yield, which, by dehydration and subsequent treatment with mineral acid, was converted into the triene aldehyde (XIII). This on condensation with malonic acid gave the tetraene acid (XIV).

$$\underset{\text{(XI)}}{MeO{\cdot}CH_2{\cdot}C(Me)(OH){\cdot}C{:}C{\cdot}C{:}C{\cdot}C(Me)(OH){\cdot}CH_2{\cdot}OMe} \longrightarrow \underset{\text{(XII)}}{MeO{\cdot}CH_2{\cdot}C(Me)(OH){\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}C(Me)(OH){\cdot}CH_2{\cdot}OMe}$$

$$\longrightarrow \underset{\text{(XIII)}}{MeO{\cdot}CH_2{\cdot}C(Me){:}CH{\cdot}CH{:}CH{\cdot}CH{:}C(Me){\cdot}CHO} \longrightarrow \underset{\text{(XIV)}}{MeO{\cdot}CH_2{\cdot}C(Me){:}CH{\cdot}CH{:}CH{\cdot}CH{:}C(Me){\cdot}CH{:}CH{\cdot}CO_2H}$$

Experimental

Light-absorption data, the majority of which are given in the Table, were determined in alcohol, unless otherwise stated.

Methoxyacetone.—1-Methoxypropan-2-ol (Reeves and Sadle, *J. Amer. Chem. Soc.*, 1950, **72**, 1252) was oxidised by Mariella and Leech's method (*ibid.*, 1949, **71**, 3558). The product was fractionally distilled through a Stedman column (12 × 1″), and the fraction of b. p. 113—114° was collected. This was estimated, by conversion of an aliquot into the 2 : 4-dinitrophenylhydrazone (cf. Iddles and Jackson, *Ind. Eng. Chem.*, 1934, **6**, 456), to contain 85% of methoxyacetone, and was used without further purification.

Acetylenic Alcohols from Methoxyacetone.—A slight excess of the acetylene was added to a stirred solution (*ca.* 1M) of ethylmagnesium bromide in ether, and the mixture was heated under reflux for 3 hr. and then cooled. Methoxyacetone in ether (2 vols.) was added dropwise, and the mixture was heated under reflux for *ca.* 2 hr. and then cooled. The Grignard complex was decomposed by the addition of saturated aqueous ammonium chloride, and the product was isolated in the usual way.

Hex-1-yne (24 g.) and methoxyacetone (20 g.) gave **1-*methoxy*-2-*methyloct*-3-*yn*-2-*ol*** (24 g.), b. p. 106—108°/18 mm., n_D^{24} 1·4474 (Found: C, 70·0; H, 10·35. $C_{10}H_{18}O_2$ requires C, 70·6; H, 10·7%).

Phenylacetylene (50 g.) and methoxyacetone (44 g.) gave **1-*methoxy*-2-*methyl*-4-*phenylbut*-3-*yn*-2-*ol*** (48 g.), b. p. 148°/13 mm., n_D^{22} 1·5448 (Found: C, 75·9; H, 7·5. $C_{13}H_{14}O_2$ requires C, 75·8; H, 7·4%). Light absorption: see Table.

1-Ethynyl*cyclo*hexene (53 g.) and methoxyacetone (47 g.) gave **4-cyclo*hex*-1′-*enyl*-1-*methoxy*-2-*methylbut*-3-*yn*-2-*ol*** (67 g.), b. p. 114—116°/2 mm., n_D^{22} 1·5032 (Found: C, 74·3; H, 9·6. $C_{12}H_{18}O_2$ requires C, 74·2; H, 9·3%). Light absorption: see Table.

	$\lambda_{max.}$, Å	$\varepsilon_{max.}$
PhC≡C·CMe(OH)·CH_2·OMe	2400	20,000
	2450	17,500
	2510	18,500
PhCH:CH·CMe(OH)·CH_2·OMe (*trans*)	2420, 2530	16,000
PhCH:CH·CMe_2·OH [1]	2510	17,500
	2560	16,500
—C≡C·CMe(OH)·CH_2·OMe	2270	10,000
—CH:CH·CMe(OH)·CH_2·OMe	2270	27,000
	2340 *	23,500
—CH:CH·CHMe·OH [2]	2330	24,300
—CH·CH:CMe·CHO + —CH_2·CH:CMe·CHO	2270	3,000
	2810, 2900	22,000
—CH·CH:CH·CHO [3]	2900	—
MeO·CH_2·CMe(OH)·C≡C·C≡C·CMe(OH)·CH_2·OMe	2280, 2420, 2510	450
HO·CHMe·C≡C·C≡C·CHMe·OH [4]	2320	320
	2425	330
	2560	210
MeO·CH_2·CMe(OH)·CH:CH·CH:CH·CMe(OH)·CH_2·OMe	2270	34,500
HO·CHMe·CH:CH·CH:CH·CHMe·OH [5] (m. p. 45°)	2270	32,000
	2340 *	24,500
MeO·CH_2·CMe:CH·CH:CH·CH:CMe·CHO	3230	28,500
CHMe:CH·CH:CH·CMe:CH·CHO [6]	3220	30,500
MeO·CH_2·CMe:CH·CH:CH·CH:CMe·CH:CH·CO_2H	3330	48,000
MeCH:CH·CH:CH·CH:CH·CH:CH·CO_2H [7]	3320 †	49,000

* Inflexion. † In hexane.

[1] Braude and Timmons, *J.*, 1950, 2001. [2] Chanley and Sobotka, *J. Amer. Chem. Soc.*, 1949, **71**, 4140. [3] Bohlmann, *Chem. Ber.*, 1951, **84**, 544. [4] Armitage, Cook, Entwistle, Jones, and Whiting, *J.*, 1952, 2003. [5] Ahmad, Sondheimer, Weedon, and Woods, *J.*, 1952, 4089. [6] Weedon and Woods, *J.*, 1951, 2687. [7] Hausser, Smakula, Kuhn, and Hoffer, *Z. physikal. Chem.*, 1935, **29**, *B*, 371.

1-*Methoxy*-2-*methyloct*-3-*en*-2-*ol* (VI; R = Bu^n).—A solution of 1-methoxy-2-methyloct-3-yn-2-ol (15 g.) in ethyl acetate (75 c.c.) was shaken in hydrogen in the presence of palladium–calcium carbonate (5 g.; 0·3% Pd). When 1 mol. of hydrogen (1980 c.c. at 15°/752 mm.) had been absorbed, the catalyst and solvent were removed and the residue was distilled, giving the *alcohol* (12·5 g.), b. p. 99°/16 mm., n_D^{18} 1·4402 (Found: C, 69·45; H, 11·7. $C_{10}H_{22}O_2$ requires C, 69·75; H, 11·65%).

2-*Methyloct*-2-*en*-1-*al* (VIII; R = Bu^n).—Toluene-*p*-sulphonic acid (60 mg.) was added to a boiling solution of the preceding alcohol (6 g.) in dry benzene (40 c.c.). A vigorous reaction occurred and the water liberated was removed by azeotropic distillation. The solution was heated under reflux for a further 15 min. and then cooled, washed with a saturated solution of sodium hydrogen carbonate, dried, and evaporated. Distillation of the residue gave the crude methoxy-diene (2·5 g.), b. p. 70—72°/15 mm., n_D^{18} 1·4587, which, in ether (15 c.c.), was shaken

with N/5-hydrochloric acid (15 c.c.) for 1 hr. The crude aldehyde was isolated, and the main bulk was converted into the *semicarbazone* (1·7 g.) which crystallised from alcohol in plates, m. p. 159° (Found: N, 21·45. $C_{10}H_{19}ON_3$ requires N, 21·35%). Light absorption: maximum, 2650 Å; $\varepsilon = 28{,}000$. The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in red needles, m. p. 121° (Found: C, 55·95; H, 6·4. $C_{15}H_{20}O_4N_4$ requires C, 56·25; H, 6·3%). Light absorption in $CHCl_3$ (main band only): maximum, 3800 Å; $\varepsilon = 28{,}000$.

1-*Methoxy*-2-*methyl*-4-*phenylbut*-3-*en*-2-*ol* (VI; R = Ph).—(*a*) A solution of 1-methoxy-2-methyl-4-phenylbut-3-yn-2-ol (10 g.) in ether (75 c.c.) was added during ½ hr. to a stirred solution of lithium aluminium hydride (2·4 g.) in ether (200 c.c.). The mixture was heated under reflux for 3 hr. and then cooled. Ethyl acetate was added followed by a saturated aqueous solution of ammonium chloride. Isolation of the product with ether gave the trans-*alcohol* (8·9 g.), b. p. 114—115°/1 mm., n_D^{20} 1·5449 (Found: C, 75·0; H, 8·45. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·35%). Light absorption: see Table.

(*b*) A product (21 g.) which possibly contained some of the *cis*-isomer, was obtained by partial catalytic reduction of the acetylenic alcohol (25 g.) in ethyl acetate (120 c.c.) over a palladium–calcium carbonate catalyst (5 g.; 0·3% Pd). It had b. p. 104—106°/0·2 mm., n_D^{18} 1·5399 (Found: C, 74·55; H, 8·55%). Light absorption: maxima, 2420 and 2510 Å; $\varepsilon = 12{,}000$.

2-*Methyl*-4-*phenylbut*-2-*en*-1-*al*.—Toluene-*p*-sulphonic acid (150 mg.) was added to a boiling solution of 1-methoxy-2-methyl-4-phenylbut-3-en-2-ol (15 g.; prepared by method *b*) in toluene (110 c.c.). A vigorous reaction occurred, the water formed was removed by azeotropic distillation, and the mixture was then boiled for a further 15 min. Isolation and distillation of the product gave an oil (3·9 g.), b. p. 83—84°/1 mm. Light absorption: maxima, 2270, 2360, 2510, and 2800 Å; $E^{1\%}_{1\text{ cm.}} = 650$, 480, 350, and 350, respectively. Hydrolysis as described above yielded the aldehyde. This was converted into the semicarbazone (3·2 g.), which crystallised from alcohol in plates, m. p. 176° (Found: N, 19·35. Calc. for $C_{12}H_{15}ON_3$, N, 19·35%). Linnell and Shen, *J. Pharm. and Pharmacol.*, 1949, **1**, 917, give m. p. 178—179°. Light absorption: maximum, 2640 Å; $\varepsilon = 23{,}000$. Inflexions, 2580, 2680, and 2760 Å; $\varepsilon = 19{,}000$, 19,000, and 14,500 respectively. (*Idem, loc. cit.*, give maximum, 2660 Å; $\varepsilon = 34{,}000$.) The 2 : 4-dinitrophenylhydrazone crystallised from alcohol as orange needles, m. p. 193° (Found: N, 16·25. Calc. for $C_{12}H_{16}O_4N_4$: N, 16·45%). (*Idem, loc. cit.*, give m. p. 188—190°.) Light absorption in $CHCl_3$ (main band only): maximum, 3780 Å; $\varepsilon = 35{,}500$.

Similarly the alcohol (7 g.; prepared by method *a*) was converted into the aldehyde semicarbazone (1·2 g.), m. p. and mixed m. p. 176°.

4-cyclo*Hex*-1′-*enyl*-1-*methoxy*-2-*methylbut*-3-*en*-2-*ol* (VI; R = *cyclo*hexenyl).—Reduction of 4-*cyclo*hex-1′-enyl-1-methoxybut-3-yn-2-ol (62 g.) in ether (1 l.) with lithium aluminium hydride (15·5 g.), and isolation of the product, gave an oil (61 g.), n_D^{19} 1·5094. Light absorption: maxima, 2270 and 2360 Å; $E^{1\%}_{1\text{ cm.}} = 1260$ and 1180, respectively, indicating a purity of *ca.* 90%. Distillation of a small portion gave the *alcohol*, b. p. 104°/0·5 mm., n_D^{22} 1·5068 (Found: C, 73·1; H, 10·15. $C_{12}H_{20}O_2$ requires C, 73·4; H, 10·25%). Light absorption: see Table.

4-cyclo*Hex*-1′-*enyl*-2-*methylbut*-2 : 4-*dien*-1-*al* (VIII; R = *cyclo*hexenyl).—A saturated solution of toluene-*p*-sulphonic acid (250 mg.) in warm toluene (70 c.c.) was added to a solution of the preceding alcohol (7·5 g.) in toluene (60 c.c.). The mixture was rapidly boiled and then immediately cooled (ice-bath). Isolation and hydrolysis of the product in the usual way gave the *aldehyde* (2·5 g.), b. p. 87—90°/10^{-2} mm., n_D^{22} 1·5710 (Found: C, 80·15; H, 9·7. $C_{11}H_{14}O$ requires C, 80·5; H, 9·8%). Light absorption: see Table. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in dark red prisms, m. p. 214° (Found: N, 16·35. $C_{17}H_{20}O_4N_4$ requires N, 16·3%). Light absorption in $CHCl_3$ (main band only): maximum, 4050 Å; $\varepsilon = 41{,}500$. The *semicarbazone* crystallised from alcohol in plates, m. p. 169° (Found: N, 19·0. $C_{12}H_{19}ON_3$ requires N, 19·0%). Light absorption: maximum, 3050 Å; $\varepsilon = 51{,}500$.

1 : 8-*Dimethoxy*-2 : 7-*dimethylocta*-3 : 5-*diyne*-2 : 7-*diol* (XI).—A solution of 1-methoxy-2-methylbut-3-yn-2-ol (10 g.) (Inhoffen, Bohlmann, Bartram, Rummert, and Pommer, *Annalen*, 1950, **570**, 54) in alcohol (10 c.c.) was added to one of cuprous ammonium chloride (from 2·5 g. of cuprous chloride and 8·0 g. of ammonium chloride) in 0·08N-hydrochloric acid (40 c.c.). The mixture was shaken in an atmosphere of oxygen until 1 mol. had been absorbed (cf. Armitage, Cook, Entwistle, Jones, and Whiting, *J.*, 1952, 2003). The inorganic green precipitate was dissolved by the addition of dilute hydrochloric acid, and the resulting solution was extracted with ether (constant ether extractor, 48 hr.). Evaporation of the extract and distillation of the residue gave the *glycol* (7·0 g.), b. p. 100—110° (bath-temp.)/10^{-4} mm., n_D^{22} 1·5095 (Found: C, 63·35; H, 8·15. $C_{12}H_{18}O_4$ requires C, 63·7; H, 8·0%). Light absorption: see Table.

The same yield of glycol was obtained by aerial oxidation of the alcohol at 55—60° in the presence of a large excess of aqueous cuprous ammonium chloride (cf. Bowden, Heilbron, Jones, and Sargent, *J.*, 1947, 1579).

1 : 8-*Dimethoxy*-2 : 7-*dimethylocta*-3 : 5-*diene*-2 : 7-*diol* (XII).—A solution of the preceding glycol (15 g.) in ether (200 c.c.) was added dropwise to one of lithium aluminium hydride (7·8 g.) in ether (800 c.c.), and the mixture was heated under reflux for 15 hr. Isolation of the product in the usual manner gave the *glycol* (12·5 g.), b. p. 100° (bath-temp.)/10^{-4} mm., m. p. 83—85°. Crystallisation from benzene gave needles, m. p. 84—86° (Found : C, 62·85; H, 9·65. $C_{12}H_{20}O_4$ requires C, 62·6; H, 9·55%). Light absorption : see Table.

8-*Methoxy*-2 : 7-*dimethylocta*-2 : 4 : 6-*trien*-1-*al* (XIII).—A solution of toluene-*p*-sulphonic acid (250 mg.) in warm toluene (100 c.c.) was added to one of the preceding glycol (10 g.) in toluene (200 c.c.). The mixture was rapidly boiled and then cooled immediately (ice-bath). Isolation of the product and hydrolysis gave the *aldehyde* (6·3 g.), b. p. 100—102°/0·5 mm., n_D^{25} 1·6015—1·6049 (Found : C, 72·9; H, 9·0. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·9%). Light absorption : see Table. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in dark red prisms, m. p. 171° (Found : N, 15·45. $C_{17}H_{20}O_5N_4$ requires N, 15·5%). Light absorption in $CHCl_3$ (main band only) : maximum, 4070 Å; $\varepsilon = 39{,}500$. The *semicarbazone* crystallised from alcohol in pale yellow plates, m. p. 180—182° (Found : N, 17·35. $C_{12}H_{19}O_2N_3$ requires N, 17·7%). Light absorption : maximum, 3280 Å; $\varepsilon = 51{,}000$.

4 : 9-*Dimethyl*-10-*methoxydeca*-2 : 4 : 6 : 8-*tetraenoic Acid* (XIV).—Malonic acid (0·9 g.) and a solution of the preceding aldehyde (0·9 g.) and freshly distilled piperidine (2 drops) in pyridine (9 c.c.) were heated on a steam-bath for 2 hr. The resulting dark red solution was cooled, acidified, and extracted with ether. Evaporation of the extract gave an oil which partly solidified when scratched. The solid (20 mg.), m. p. 150—153°, was crystallised from benzene, giving the *acid* as yellow needles, m. p. 159° (Found : C, 69·8; H, 8·35. $C_{13}H_{18}O_3$ requires C, 70·2; H, 8·15%). Light absorption : see Table.

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436. *The Oxidation of Carboxylic Acids Containing a Tertiary Carbon Atom.*

By J. Kenyon and M. C. R. Symons.

Contrary to the commonly held view, hydroxy-carboxylic acids $RR'C(OH)\cdot[CH_2]_n\cdot CO_2H$ are obtained from the corresponding branched-chain carboxylic acids by potassium permanganate in dilute alkaline solution only in limited yield and only when $n = 2$. When $n = 0$ or 2, the use of permanganate in *concentrated* alkaline solution gives yields of 50—90%. When $n = 2$, replacing permanganate by manganate in dilute alkaline solution gives the hydroxy-acids in 70—80% yield. Neither procedure leads to β-hydroxy-acids.

For study of the mechanism of replacement by hydroxyl of a hydrogen atom attached to a tertiary carbon atom, a reaction was chosen which is given in many textbooks as a general method for the preparation of hydroxy-carboxylic acids (*e.g.*, Rodd, "Chemistry of Carbon Compounds," Elsevier, Amsterdam, 1951, p. 780), namely, the oxidation of branched-chain carboxylic acids by the use of potassium permanganate in dilute alkaline solution :

$$RR'CH\cdot[CH_2]_n\cdot CO_2H \longrightarrow RR'C(OH)\cdot[CH_2]_n\cdot CO_2H$$

The factual basis for this general method is, however, somewhat slender. Hydroxy-acids constitute only a small part of the oxidation products of branched-chain carboxylic

acids (Meyer, *Annalen*, 1883, **219**, 234; **220**, 1; Miller, *ibid.*, 1880, **200**, 261; Ladenburg and Rugheimer, *Ber.*, 1880, **13**, 373; Fittig and Bredt, *Annalen*, 1881, **208**, 59; Fittig and Thron, *ibid.*, 1899, **304**, 285), and, since 1899, only two references to the use of this reaction have been found, neither of which reports the formation of the expected products (Lawrence, *J.*, 1899, 531; *Proc.*, 1900, 1541; 1901, **47**; Linstead and Mann, *J.*, 1930, 2064).

Nevertheless, attempts have been made to convert several carboxylic acids into the corresponding hydroxy-acids by the use of the prescribed reagents (see 3rd col. of Table).

Oxidation of carboxylic acids to hydroxy-carboxylic acids.

		Yield (%) of hydroxy-acid by use of		
No.	Acid oxidized	$KMnO_4$ in dil. NaOH	$KMnO_4$ in conc. NaOH	K_2MnO_4 in dil. NaOH
1	$CHMeEt{\cdot}CO_2H$	trace	80	0
2	$CHMePh{\cdot}CO_2H$	,,	90	0
3	$CHMe_2{\cdot}CH_2{\cdot}CO_2H$	0	0	0
4	$CHMeEt{\cdot}CH_2{\cdot}CO_2H$	0	0	0
5	$CHMeEt{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$	10	70	80
6	$CHMePh{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$	10	50	70
7	$CHMeBu{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$	—	60	70

Acids nos. 1, 4, 5 underwent little or no oxidation with the following reagents: H_2O_2 (30%) in H_2O, AcOH, or $H{\cdot}CO_2H$: $K_2Cr_2O_7$ in dil. H_2SO_4 at 100°: $KMnO_4$ in boiling $COMe_2$ for 12 hr. Acid no. 2 underwent rapid reaction with Fenton's reagent at room temperature with copious evolution of CO_2: acetophenone (20%) and unchanged material (50%) were isolated. Acids nos. 1 and 5 appeared to be completely degraded to CO_2 by CrO_3 in AcOH and Ac_2O.

In each instance, a quantity of potassium permanganate was consumed equivalent to that required for the oxidation of the acid to the corresponding hydroxy-acid but only very small quantities of the corresponding α-hydroxy-acids, no β-hydroxy-acids, and less than 10% of the theoretical quantity of γ-hydroxy-acids could be isolated. The formation of large quantities of carbonate, and the recovery of about 50% of unchanged starting material, showed that the main oxidation was deep-seated and that the reaction is unsatisfactory as a general preparative method. Experiments at lower temperatures and greater dilutions were no more satisfactory.

Numerous attempts to effect the desired type of oxidation by other oxidants were uniformly unsuccessful (see footnotes to Table). The conditions employed for oxidation with potassium dichromate were similar to those used by Lawrence (*J.*, 1899, 531), in the conversion of *iso*propylsuccinic acid into terebic acid and of *iso*propylglutaric acid into terpenylic acid, but differed in that the reaction mixture was not homogeneous.

Accordingly, attention was again directed to potassium permanganate in alkaline solution. Since the required oxidation represents a two-electron change (as distinct from the reduction of permanganate to manganese dioxide, which is a three-electron change), it was expected that the reaction process might be considerably simplified by (*a*) greatly increasing the concentration of alkali so that the permanganate could be reduced only as far as manganate (a one-electron change) and (*b*) using potassium manganate in dilute alkaline solution (reduction to manganese dioxide is then a two-electron change). Each of these modifications proved partly successful (see Table): method (*a*) gave very good yields of α- and γ-hydroxy-acids, but still no β-hydroxy-acids; method (*b*) gave good yields of γ-hydroxy-acids but no α- or β-hydroxy-acids. The most satisfactory method of preparing γ-hydroxy-acids from γ-branched-chain carboxylic acids is by a combination of the two procedures. This differs from the more usual oxidation with potassium permanganate in dilute alkaline solution in that, by suitable adjustment of the concentration of alkali, the two stages in reduction ($MnO_4' \longrightarrow MnO_4'' \longrightarrow MnO_2$) are consecutive and not simultaneous.

The failure to isolate even small quantites of β-hydroxy-acids may be due to the ready formation of substituted acrylic acids, which would rapidly be oxidised further under the conditions employed. The isolation of ketones RR'CO and large quantities of carbon dioxide from the products supports this suggestion.

Experimental

Preparation of Branched-chain Carboxylic Acids.—α-Methylbutyric acid, prepared in 61% yield from malonic ester, had b. p. 63—64°/2 mm. (Found: equiv., 102·3. Calc. for $C_5H_{10}O_2$: equiv., 102); its *p*-bromophenacyl ester had m. p. 54·5° (Kenyon and Ross, *J.*, 1951, 3410, give m. p. 55°).

β-Methylvaleric acid, similarly prepared in 65% yield, had b. p. 63°/1 mm. (Found: equiv., 115·8. Calc. for $C_6H_{12}O_2$: equiv., 116); its *p*-bromophenacyl ester had m. p. 36·5° (Sabetay and Panouse, *Compt. rend.*, 1947, **225**, 887, give m. p. 36°).

4-Methylhexanoic acid, prepared in 53% yield, had b. p. 85°/2 mm. (Found: equiv., 130. Calc. for $C_7H_{14}O_2$: equiv., 130); its p-*bromophenacyl* ester formed plates, m. p. 63—64° (Found: Br, 24·55. $C_{15}H_{19}O_3Br$ requires Br, 24·4%); its S-*benzylthiuronium* salt formed plates, m. p. 142° (Found: N, 9·65. $C_{15}H_{24}O_2N_2S$ requires N, 9·5%).

4-Methyloctanoic acid was prepared from 4-hydroxy-4-methyloctanoic lactone (see below) by Cason's procedure (*J. Amer. Chem. Soc.*, 1944, **66**, 1764). The lacton e(18 g.) and thionyl chloride (50 g.) in benzene (30 c.c.) were heated under reflux for 3 hr., then mixed with absolute ethanol (100 c.c.) and saturated at 0° with hydrogen chloride. Distillation of the product yielded ethyl 4-methyloctenoate (41·1 g.), b. p. 76—79°/3 mm., together with unchanged lactone (2 g.), b. p. 90—93°/2 mm. Hydrogenation of this (10 g.) in absolute ethanol (100 c.c.) at low pressure in the presence of platinum oxide (0·15 g.) during 0·5 hr. gave the saturated ester (7·9 g.; b. p. 108°/2 mm.) and thence by hydrolysis 4-methyloctanoic acid (6 g.), b. p. 110°/2 mm. (Found: equiv., 158·3. Calc. for $C_9H_{18}O_2$: equiv., 158). The S-*benzylthiuronium* salt formed needles, m. p. 135° (Found: N, 8·7. $C_{17}H_{28}O_2N_2S$ requires 8·65%).

α-Phenylpropionic acid (Campbell and Kenyon, *J.*, 1946, 25) gave a S-*benzylthiuronium* salt, plates, m. p. 146° (Found: N, 8·9. $C_{19}H_{24}O_2N_2S$ requires 8·9%).

α-Phenylpropionic acid (15 g.) in ethereal solution was reduced by lithium aluminium hydride (4·75 g.), and the resulting hydratropyl alcohol (11·9 g.; b. p. 62—63°/0·1 mm.) converted by phosphorus tribromide into hydratropyl bromide (12·6 g.; b. p. 49°/0·1 mm.), which, by condensation with malonic ester in the usual way, afforded γ-phenyl-*n*-valeric acid (5·6 g.), b. p. 98°/0·1 mm. [S-*benzylthiuronium* salt, plates, m. p. 134° (Found: N, 8·1. $C_{19}H_{24}O_2N_2S$ requires N, 8·1%)].

Preparation of Hydroxy-acids and Lactones.—α-Hydroxy-α-methylbutyric acid, prepared from ethyl methyl ketone (*via* the bisulphite compound and the cyanohydrin) in 63% yield, had b. p. 117·5°/12 mm., m. p. 69·5—70·5° (after sublimation) (Found: equiv., 117·2. Calc. for $C_5H_{10}O_3$: equiv., 118).

β-Hydroxy-β-methyl-*n*-valeric acid, prepared from ethyl bromoacetate and ethyl methyl ketone in 68% yield, had b. p. 138—139°/18 mm. (Found: equiv., 131·3. Calc. for $C_6H_{12}O_3$: equiv., 132).

4-Hydroxy-4-methylhexanoic lactone, prepared from ethylmagnesium bromide and ethyl lævulate by Cason's method (*loc. cit.*) in 61% yield; had b. p. 73°/0·5 mm. (Found: equiv., 127·6. Calc. for $C_7H_{12}O_2$: equiv., 128). The S-*benzylthiuronium* salt of the hydroxy-acid formed plates, m. p. 142° (Found: N, 9·4. $C_{15}H_{24}O_3N_2S$ requires N, 9·0%).

Atrolactic acid, prepared from acetophenone in 61% yield, had, after sublimation, m. p. 91·3—91·6° (Found: equiv. 165·7. Calc. for $C_9H_{10}O_3$: equiv., 166); its S-*benzylthiuronium* salt formed plates, m. p. 160° (Found: N, 8·6. $C_{17}H_{20}O_3N_2S$ requires N, 8·4%).

4-Hydroxy-4-methyloctanoic lactone, prepared from *n*-butylmagnesium bromide and ethyl lævulate in 60% yield, had b. p. 84°/1 mm. (Found: equiv., 156. Calc. for $C_9H_{16}O_2$: equiv., 156); the S-*benzylthiuronium* salt of the hydroxy-acid formed needles, m. p. 116·5—117° (Found: N, 8·25. $C_{17}H_{28}O_3N_2S$ requires N, 8·3%).

γ-Phenyl-γ-valerolactone, prepared from phenylmagnesium bromide and ethyl lævulate in 45% yield, had b. p. 123°/1 mm. The hydroxy-acid, obtained as a precipitate from an aqueous solution of its sodium salt on acidification at 0°, separated from light petroleum in needles, m. p. 103·5—104° (Found: equiv., 194·3. Calc. for $C_{11}H_{14}O_3$: equiv., 194); its S-*benzylthiuronium* salt formed plates, m. p. 127° (Found: N, 7·8. $C_{19}H_{24}O_3N_2S$ requires N, 7·8%).

Oxidations.—"AnalaR" potassium permanganate and sodium or potassium hydroxide were used. The products were identified by conversion into the *p*-bromophenacyl esters or benzylthiuronium salts (mixed m. p. determinations).

(a) *With potassium permanganate in dilute alkaline solution.* In earlier experiments, the general procedure recommended by Meyer (*loc. cit.*) was followed. In later experiments, vari-

ations of temperature and concentration were made but only 4-methylhexanoic acid underwent oxidation in the desired way, to give 4-hydroxy-4-methylhexanoic lactone in 8·6% yield. In all cases, much unchanged material was recovered, with carbon dioxide and other products of deep-seated oxidation. The results are in the Table.

(b) *With potassium manganate in dilute alkaline solution.* The following general procedure was adopted. Potassium manganate was prepared by heating a solution of potassium permanganate (6·3 g., 0·04 mol.) and potassium hydroxide (40 g.) in water (150 c.c.) on a steam-bath until the solution became green (30 min.). The cooled solution was partly neutralised with sulphuric acid (100 c.c.; 6N), the carboxylic acid (0·04 mol.) added, and the green solution kept at 90° until the green colour was discharged (10—30 min.). After removal of manganese dioxide, the solution was extracted with ether, and the aqueous layer acidified and again extracted with ether. This extract was dried ($MgSO_4$), the solvent evaporated off, and the product distilled under reduced pressure. When γ-hydroxy-acids were formed, the product was kept in a desiccator *in vacuo* over potassium hydroxide in order to convert them into lactones. The crude lactone was exhaustively shaken with saturated sodium hydrogen carbonate solution and then with ether. The ethereal layer was washed with water, dried ($MgSO_4$), and freed from solvent. The aqueous layer was acidified and treated in like manner. The results are in the Table.

(c) *With potassium permanganate in concentrated alkaline solution.* The following general procedure was adopted. The acid (0·02 mol.) in water (50 c.c.) containing potassium hydroxide (40 g.) was vigorously shaken with a solution (100 c.c.) of potassium permanganate (6·3 g., 0·04 mol.) and potassium hydroxide (20 g.), added drop-wise at 40° (± 1°) during about 20 min. The resulting green solution was cooled in ice and shaken with sulphur dioxide until colourless, after which the manganese dioxide was removed. The products were isolated, as in (b) above. The results are in the Table.

(d) *Oxidation of γ-branched-chain acids by procedures* (b) *and* (c) *consecutively.* A solution of the acid (0·02 mol.) and potassium hydroxide (40 g.) in water (50 c.c.) was vigorously shaken at 40° with a solution (100 c.c.) containing potassium permanganate (2·1 g., 0·0167 mol.) and potassium hydroxide (6 g.), added drop-wise during *ca.* 6 min. The resulting green solution was partly neutralised with sulphuric acid (100 c.c.; 6N) and kept at 90° during 10 min., by which time the green colour was discharged. The products were isolated as in (b) above, the yields of γ-hydroxy-acids being between 70 and 80%.

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437. *Protozoal Polysaccharides. Structure of the Polysaccharide produced by the Holotrich Ciliates present in Sheep's Rumen.*

By G. FORSYTH and E. L. HIRST.

The holotrichously ciliated protozoa present in the rumen of sheep synthesise *in vivo* and *in vitro* an intracellular storage polysaccharide from glucose, fructose, or sucrose. This polysaccharide is stained reddish-purple by iodine, contains only glucose residues, and has a high molecular weight. It has one terminal glucose residue for every 22 glucose residues in the molecule. The unit chains, of average chain length 22, consist of α-1 : 4-linked D-glucose residues and are united by $C_{(1)}$–$C_{(6)}$ linkages. The amylose content is negligible and the polysaccharide therefore has a highly branched molecular structure closely similar to that of amylopectin.

SOME protozoa are known to synthesis polysaccharides of the glucosan type. One such, from *Tetrahymena piriformis*, has been examined by Manners and Ryley (*Biochem. J.*, 1952, **52**, 480) who found it to be structurally similar to animal glycogen, with a unit chain length of 13 α-linked glucose residues and a molecular weight of about 10^7. Another, found in the ciliate *Cycloposthium* present in the colon and cæcum of a horse, has a different structure, resembling that of amylopectin. This polysaccharide has a unit chain length of 23 α-linked glucose residues and a molecular weight of 200,000 or more (Forsyth, Hirst, and Oxford, preceding paper). It has been found recently by Oxford that the holo-

trichously ciliated protozoa [*Isotricha* (two species) and *Dasytricha* (one species)] present in sheep's rumen and found nowhere in Nature but in ruminants, can ferment either *in vitro* or in the rumen glucose, fructose, or sucrose, but not (*in vitro* at any rate) other simple sugars such as glucuronolactone, mannose, galactose, xylose, arabinose, sorbose, lactose, and maltose. During the process these protozoa store immense numbers of granules of a glucose-containing polysaccharide which is stained purple with iodine (Oxford, *J. Gen. Microbiol.*, 1951, **5**, 83). The chemical structure of this material forms the subject of the present paper and the results show that here again the polysaccharide is closely similar to amylopectin in possessing a unit chain length of 23 α-linked glucose residues, a highly branched structure, a high molecular weight, and a high intrinsic viscosity in solution.

We are indebted to Dr. Oxford for a supply of the polysaccharide which had been liberated as granules when the cells of the protozoa were disrupted by shaking them with a buffered solution of " Teepol XL " (Oxford, *loc. cit.*). In bulk these granules formed a greyish-white powder which on acid hydrolysis gave glucose as the only sugar. For subsequent investigations the material was purified by the chloral hydrate method (Meyer and Bernfeld, *Helv. Chim. Acta*, 1940, **23**, 875) and was obtained as a colourless powder. It gave a purple colour with iodine. The absence of material of the amylose type was shown by the low " blue value " (0·5) (Hassid and McCready, *J. Amer. Chem. Soc.*, 1943, **65**, 1154; Haworth, Peat, Bourne, and Macey, *J.*, 1948, 924), the results of potentiometric iodine titration (see the Experimental section), and the negative results obtained on application of the Nussenbaum test for amylose (*Analyt. Chem.*, 1951, **23**, 1478). Only glucose was obtained on hydrolysis.

Acetylation of the polysaccharide, carried out by the mild method of Pacsu and Mullen, gave a triacetate which was indistinguishable from acetylated amylopectin and had a high intrinsic viscosity in *m*-cresol. The trimethyl derivative of the polysaccharide was prepared by the action of methyl sulphate and aqueous sodium hydroxide in an atmosphere of nitrogen, followed by methylation in liquid ammonia by Freudenberg and Boppel's method (*Ber.*, 1938, **71**, 2527). It appeared that methylation to a methoxyl content of 44% could be effected by this procedure without appreciable degradation of the molecule. The trimethyl derivative had $\eta_{sp.}/c$ 1·42 in *m*-cresol, corresponding to a molecular weight of *ca.* 170,000, the constant given by Hirst and Young (*J.*, 1939, 1471) being used.

After methanolysis of the trimethyl derivative with methyl alcohol containing hydrogen chloride, followed by acid hydrolysis of the methylated methyl glucoside so obtained, paper partition chromatography revealed the presence of four substances corresponding in R_G values with 2 : 3 : 4 : 6-tetramethyl glucose, 2 : 3 : 6-trimethyl glucose, and two dimethyl glucoses. Quantitative results showed that the yield of tetramethyl glucose was 5·3%, equivalent to the presence of one non-reducing terminal glucose residue for every 21 glucose residues in the molecule. The experiment was then repeated on a larger scale, the methylated glucoses being separated by partition chromatography. Crystalline 2 : 3 : 4 : 6-tetramethyl D-glucose was obtained in yield corresponding to a unit chain length of 22 glucose residues in the polysaccharide. The identity of the 2 : 3 : 6-trimethyl D-glucose was confirmed and it was proved that a considerable portion of the dimethyl glucose was the 2 : 3-derivative. Some 2 : 6-dimethyl D-glucose appeared to be present also, but the structural significance of this is uncertain since it could have arisen from incomplete methylation of the polysaccharide. Monomethyl glucoses and glucose were found only in negligible proportions.

The occurrence of 1 : 6-linkages as inter-unit bonds was further indicated by the results of oxidation with periodate. Determination of the amount of formic acid produced when the polysaccharide is oxidised by potassium metaperiodate showed that there is one non-reducing terminal glucose residue for every 22 glucose residues in the molecule. This is in agreement with the value obtained by the methylation method and proves the absence of glucose residues linked solely through $C_{(1)}$ and $C_{(6)}$. The absence of glucose amongst the products obtained by hydrolysis of the periodate-oxidised polysaccharide shows that by far the most, if not all, of the inter-unit bonds are of the 1 : 6-type. Linkages of the $C_{(1)}$–$C_{(2)}$ or $C_{(1)}$–$C_{(3)}$ type must be almost totally absent.

This evidence points to a molecular structure for this protozoal polysaccharide very similar to that of amylopectin. The molecule must be highly branched and consists of a large number of units chains, each containing on an average 22 α-1 : 4-linked glucopyranose residues, the unit chains themselves being joined at some point (or points) in their length by 1 : 6-glucosidic linkages. The molecular structure is therefore strikingly similar to that found to be present in the polysaccharide produced by *Cycloposthium* in the colon and cæcum of the horse.

Experimental

Whatman No. 1 filter paper was used for chromatography, with butanol–light petroleum saturated with water as mobile phase, unless otherwise stated. R_G values refer to rates relative to that of tetramethyl glucose.

Purification of the Polysaccharide.—The material was provided by Dr. A. E. Oxford, Rowett Research Institute, Aberdeenshire. (For method of preparation see Masson and Oxford, *J. Gen. Microbiol.*, 1951, **5**, 664.) It was a colourless powder which gave a reddish-purple colour with iodine. After hydrolysis with acid, paper chromatography revealed that glucose only had been formed. Purification of the polysaccharide was effected by Meyer and Bernfeld's method (*loc. cit.*) using chloral hydrate. The resulting product (86% recovery) was a colourless powder which on acid hydrolysis gave 89% of the theoretical amount of glucose. The polysaccharide had $[\alpha]_D^{17}$ +171° (*c*, 1·0 in N-NaOH), $[\alpha]_D^{20}$ +201° (*c*, 0·4 in 30% $HClO_4$). The blue value, determined by Hassid and McCready's method (*loc. cit.*) as modified by Bourne, Haworth, Macey, and Peat (*loc. cit.*), was 0·049.

Potentiometric Iodine Titration of the Polysaccharide.—The method of Bates, French, and Rundle (*J. Amer. Chem. Soc.*, 1943, **65**, 142) as modified by Wilson, Schoch, and Hudson (*ibid.*, p. 1381) was used. No break in the curve of free-iodine concentration plotted against iodine uptake was found. The amylose content was therefore negligible.

Acetylation.—Pacsu and Mullen's method was used (*J. Amer. Chem. Soc.*, 1941, **63**, 1487). After two treatments the product was a colourless powder, soluble in chloroform, having $[\alpha]_D^{17}$ +168° (*c*, 1·0 in $CHCl_3$), $\eta_{sp.}/c$ 2·1 in *m*-cresol (Found: Ac, 43·9. Calc. for $C_{12}H_{16}O_8$: Ac, 44·8%).

End-group Determination by Periodate Oxidation.—The substance was treated with sodium metaperiodate and potassium chloride (Brown, Halsall, Hirst, and Jones, *J.*, 1948, 27), the acid titre after 150 hr. corresponding to the formation of 0·045 mole of formic acid from 162 g. of the polysaccharide. This corresponds to the presence of one non-reducing terminal group per 22 ± 1 glucose residues.

After completion of the formic acid determination (see above) ethylene glycol was added to the solution to destroy excess of periodate. The oxidised material was filtered off, washed with water till free from oxidant (tested with diphenylamine and sulphuric acid), and dried. It was then hydrolysed with sulphuric acid (20 c.c.; 0·5N) at 95° for 10 hr. After neutralisation with barium carbonate, followed by filtration, the solution was examined by paper chromatography for the presence of glucose. No glucose or other reducing sugar was found.

Methylation of the Polysaccharide.—The material (10 g.) was methylated under conditions similar to those used by Hirst, Jones, and Roudier (*J.*, 1948, 1779). After 37 additions of the reagents, the product showed $\eta_{sp.}^{20}/c$ 1·01 (*c*, 0·32 in *m*-cresol) (Found: OMe, 40·7%). A sample (4 g.) of this material was further methylated by Freudenberg and Boppel's method (*Ber.*, 1938, **71**, 2527) as modified by Hodge, Hilbert, and Harjala (*J. Amer. Chem. Soc.*, 1951, **73**, 3312). After three additions of sodium and methyl iodide, the product (2·9 g.) was isolated as a cream-coloured powder by precipitation from chloroform by light petroleum (b. p. 40—60°) (Found: OMe, 43·2%). This product was fractionated by the solution method, with successive mixtures of chloroform and light petroleum. The following fractions were obtained.

Fraction	Petroleum : Chloroform	Yield	OMe (%)	$[\alpha]_D^{20}$ (*c*, 1·0 in $CHCl_3$)	$\eta_{sp.}^{20}/c$ (*c*, 0·4 in *m*-cresol)
1	50 : 0	0·0024 g.	—	—	—
2	45 : 5	0·0033 g.	—	—	—
3	40 : 10	0·8490 g.	43·9	+205°	1·24
4	35 : 15	0·9390 g.	43·7	+204°	1·42
5	30 : 20	0·6940 g.	43·6	+204°	1·21
6	25 : 25	0·4420 g.	42·0	—	1·49

Hydrolysis of the Methylated Polysaccharide and Separation of Methylated Glucoses.—Fractions 3, 4, and 5 (see above) were combined (2·21 g.) and hydrolysed under reflux by boiling

methanolic hydrogen chloride (80 c.c.; 1%). After neutralisation with silver carbonate, treatment with hydrogen sulphide, filtration, and removal of the solvent, a non-reducing syrup was obtained. This was boiled under reflux with hydrochloric acid (70 c.c.; 2%) for 7 hr. After neutralisation with silver carbonate, filtration, and concentration, a syrup (1·97 g.) was obtained which partly crystallised. Preliminary analysis of a small portion by paper chromatography revealed 2 : 3 : 4 : 6-tetramethyl glucose R_G 1·0 (5·3%), 2 : 3 : 6-trimethyl glucose R_G 0·81 (84—85%), and dimethyl glucoses R_G 0·59, 0·50 (9·0—10·0%). Traces of monomethyl glucose and glucose were also observed. The yield of tetramethyl glucose indicates the presence of one non-reducing terminal group per 21 ± 1 glucose residues.

Separation of Methylated Glucoses on a Cellulose Column.—The mixture of methylated glucoses (1·13 g.) was separated on a column of powdered cellulose (powdered Whatman No. 1 ashless filter tablets; 50 × 3 cm.) in the usual way (Hough, Jones, and Wadman, *J.*, 1949, 2511; Chanda, Hirst, Jones, and Percival, *J.*, 1950, 1289). By elution with a mixture of 1 : 1 light petroleum (b. p. 100—120°)–butanol, saturated with water, fractions (1) (0·247 g.), (2) (0·688 g.), (3) (0·081 g.), and (4) (0·023 g.) were isolated. By subsequent elution with water, a further fraction was obtained which was shown by paper chromatography to contain traces of monomethyl glucose and glucose. This was not further investigated. The total recovery was 91%.

Fraction (1). Paper chromatography revealed the presence of a single spot (R_G 1·0), corresponding to tetramethyl glucose. A small portion (10 mg.) was hydrolysed with boiling sulphuric acid (2%) for 7 hr. Re-examination by paper chromatography revealed the presence of an additional substance corresponding to 2 : 3 : 6-trimethyl glucose. Fraction (1) (0·244 g.) was, therefore, hydrolysed with hydrochloric acid (10 c.c.; 1%) for 7 hr. The hydrolysate was separated on a fresh cellulose column (50 × 1·5 cm.), as before, to give fractions (1*a*) (0·051 g.) and (1*b*) 0·180 g. (recovery 94%). Fraction (1*a*) partly crystallised. After three recrystallisations from light petroleum (b. p. 40—60°) it had m. p. 85° (not depressed on admixture with authentic 2 : 3 : 4 : 6-tetramethyl D-glucopyranose), $[\alpha]_D^{18}$ +84° (*c*, 0·5 in H_2O) (Found: OMe, 52·0. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5%). The anilide had m. p. 137° (alone or admixed with authentic 2 : 3 : 4 : 6-tetramethyl D-glucose anilide) (Found: N, 4·4; OMe, 39·4. Calc. for $C_{16}H_{25}O_5N$: N, 4·5; OMe, 39·9%). From the above results it was estimated that the methylated polysaccharide contained one non-reducing terminal group per 22 ± 2 glucose units.

The combined fractions partly crystallised. The material was recrystallised from butyl acetate and had m. p. 117° (alone or admixed with an authentic sample of 2 : 3 : 6-trimethyl D-glucose), $[\alpha]_D^{16}$ +87° (initial), +69° (final) (*c*, 1·0 in H_2O), and $[\alpha]_D^{14}$ +67° (initial), −36° (12 hr.) (*c*, 1·0 in 2% methanolic hydrogen chloride) (Found: OMe, 41·5. Calc. for $C_9H_{18}O_6$: OMe, 41·9%).

Fraction (3) was a pale yellow syrup which failed to crystallise after several weeks. The R_G value (0·59) on a paper chromatogram was identical with that of 2 : 3-dimethyl D-glucose. The material had $[\alpha]_D^{15}$ +107° (initial value), +61° (final) (*c*, 1·0 in H_2O) (Found: OMe, 29·0. Calc. for $C_8H_{16}O_6$: OMe, 29·7%). On oxidation by bromine water 2 : 3-dimethyl gluconic acid was obtained and was identified as the phenylhydrazide (Evans, Levi, Hawkins, and Hibbert, *Canad. J. Res.*, 1942, **20**, *B*, 175), m. p. 160° (Found: N, 8·6; OMe, 18·9. Calc. for $C_{14}H_{22}O_6N_2$: N, 8·9; OMe, 19·7%).

Fraction (4) was a pale yellow syrup, $[\alpha]_D^{15}$ +74° (initial value), +60° (final) (*c*, 1·0 in H_2O), $[\alpha]_D^{13}$ +60° (initial value), −10° (after 12 hr.) (*c*, 0·75 in cold 2% methanolic hydrogen chloride) (Found: OMe, 28·9. Calc. for $C_8H_{16}O_6$: OMe, 29·7%). The fraction was boiled with 1% methanolic hydrogen chloride, and the mixed methyl glucosides were isolated in the usual way. This mixture was then oxidised by sodium metaperiodate (see Bell, *J.*, 1948, 992). The uptake of sodium metaperiodate was 74% of the amount required for one mol. of periodic acid per $C_9H_{18}O_6$ unit, indicating that the fraction contained approx. 74% of 2 : 6-dimethyl D-glucose.

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438. *The Formation of Phenoxyacetic Acids from Alkoxybenzenes and Diazoacetic Ester.*

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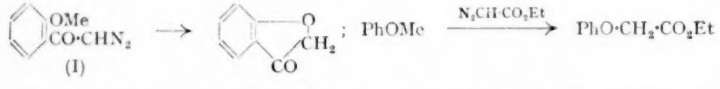
Alkoxybenzenes are partly converted with expulsion of one *O*-alkyl group into phenoxyacetic acids during Buchner-type ring-expansions with diazoacetic ester. Methylenedioxybenzene, when heated with diazoacetic ester, yields benzodioxen-2-carboxylic ester.

Recent papers from this laboratory have dealt with the conversion of alkoxybenzenes into tropolones and related compounds by ring expansion with diazoacetic ester and subsequent oxidation of the intermediate esters with bromine (Bartels-Keith, Johnson, *et al.*, *J.*, 1951, 2352; 1952, 4461). In all of these diazoacetic ester reactions, besides the required *cyclo*heptatrienecarboxylic ester, a phenoxyacetic ester was produced in yields of up to 40%, but generally 5—10%, based on the quantity of alkoxybenzene which reacted. In these reactions one of the alkyl groups of the alkoxybenzene was replaced by a carbethoxymethyl group and the possibility that such a transformation might be caused by chloroacetic ester, known to be present (up to 10%) in diazoacetic ester when prepared by Womack and Nelson's method (*Org. Syntheses*, 1944, **24**, 56) and used without distillation, was at first considered. This was disproved when similar quantities of phenoxyacetic esters were obtained from reactions with pure diazoacetic ester prepared from glycine ester in the absence of chloride ions (Skinner, *J. Amer. Chem. Soc.*, 1924, **46**, 731). Furthermore, no phenoxyacetic ester was obtained from anisole and chloroacetic ester boiling under reflux. It has been established that the carbon atom expelled in the formation of phenoxyacetic ester from anisole and diazoacetic ester is that contained in the methyl group, for a similar reaction with phenetole also gave phenoxyacetic ester together with 4-ethoxy*cyclo*hepta-1 : 3 : 5-trienecarboxylic ester (Bartels-Keith, Johnson, and Langemann, *J.*, 1952, 4461). Only very small quantities of phenolic compounds were obtained from these reactions; *e.g.*, a little *p*-hydroxyphenoxyacetic ester was isolated in the experiment with quinol dimethyl ether, and it is very unlikely that the free phenols are intermediates.

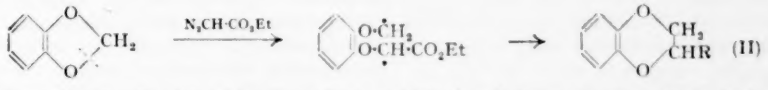
The fission of alkyl aryl ethers with diazoacetic ester is related formally to the intramolecular cyclisation of *o*-anisoyldiazomethane (I) to coumaranone and similar reactions (Pfeiffer and Enders, *Chem. Ber.*, 1951, **84**, 247; Marshall and Walker, *J.*, 1952, 467; Bose and Yates, *J. Amer. Chem. Soc.*, 1952, **74**, 4703). The cyclisation of (I) was brought about



by the action of dilute hydrochloric acid at room temperature and operates by an ionic mechanism. On the other hand, the diazoacetic ester condensations described in the present paper were carried out at 150° in the absence of solvent and a free-radical mechanism is more probable, especially as fumaric ester is frequently isolated from the reaction mixture, and phenoxyacetic ester was also produced from anisole and diazoacetic ester after irradiation with ultra-violet light. In this connection it is of interest that Seth and Deshapande (*J. Indian Chem. Soc.*, 1950, **27**, 429) have obtained a compound, not identified, by heating (I) in the absence of solvent or acid, and from the physical constants given for their product and its derivatives it is almost certainly coumaranone. There is therefore fairly good evidence that the two different mechanisms, ionic and free-radical, may operate in these condensations, and lead to the same products.

In attempts to determine the fate of the expelled alkyl radical the reaction of diazoacetic ester with the cyclic ethers chroman and methylenedioxybenzene has been examined and the crude ester mixture fractionated and converted into the corresponding acids as before. In the case of methylenedioxybenzene, the main acidic product was

identified as benzodioxen-2-carboxylic acid (II; R = CO_2H) by comparison with an authentic specimen prepared by the alkaline condensation of catechol with αβ-dibromopropionic ester. Reduction of the acid (II; R = CO_2H) with lithium aluminium hydride gave the corresponding alcohol (II; R = CH_2·OH) which has been obtained previously (J. R. Geigy, S.A., U.S.P. 2,366,102; *Chem. Abs.*, 1946, **40**, 2271). The gift of a specimen of this compound from J. R. Geigy, S.A., is gratefully acknowledged. The conversion of methylenedioxybenzene into (II; R = CO_2Et) is quite analogous to the production of phenoxyacetic ester from anisole. One of the oxygen–alkyl carbon bonds is split as the CH·CO_2Et diradical attacks the oxygen, and the resulting diradical (III) forms the dioxan ring by intramolecular addition :



On the other hand, the main crystalline acid isolated from the reaction of chroman with diazoacetic ester was a chromano*cyclo*heptatrienecarboxylic acid, the exact structure of which was not determined. The steric factors for the expansion of the six-membered heterocyclic ring are not so favourable in this case and the alternative Buchner-type ring expansion of the aromatic ring is therefore more prominent.

During this work a number of substituted phenoxyacetic acids and their derivatives were prepared and these are recorded in the Experimental section. The phenoxyacetic acids, either in dioxan solution or as Nujol mulls, showed two carbonyl bands in their infra-red spectra (Table), a feature not exhibited in the spectra of the corresponding esters. The same phenomenon was observed with methoxyacetic acid, either as a liquid film or in dioxan solution, and it seems to be a characteristic of the alkoxy- and aryloxy-acetic acids. Flett (*J.*, 1951, 962) has recorded that the infra-red spectrum of glycollic acid also shows two bands in the carbonyl region of its infra-red spectrum.

*Infra-red spectra of alkoxyacetic and aryloxyacetic acids and derivatives** (*" carbonyl region " only*).

Substituted acetic acid	Wave nos. of " carbonyl region " bands	
Methoxy- (liquid film)	1755	1725
Methoxy- (dioxan)	1761	1740
Phenoxy- (cp. Flett, *loc. cit.*)	1740	1705
o-Methoxyphenoxy-	1745	1715
m-Methoxyphenoxy-	1755	1720
m-Methoxyphenoxy- (dioxan)	1768	1742
p-Methoxyphenoxy-	1738	1710
2 : 5-Dibromo-4-methoxyphenoxy-	1760	1730
2 : 4-Dimethoxyphenoxy-, m. p. 108°	1750	1718
2 : 4-Dimethoxyphenoxy-, m. p. 121°	1750	1712
2 : 5-Dimethoxyphenoxy-	1752	1718
o-Ethoxyphenoxy-	1726	(?)1685
2 : 6-Dimethylphenoxy-	1736	(?)1710
p-Hydroxyphenoxy-	1745	1718
p-$C_6H_4(O·CH_2·CO_2H)_2$	1740	1710

* Determined as Nujol mulls except where otherwise stated.

Experimental

Diazoacetic ester and the alkoxybenzenes were condensed at 150° for 5—6 hr. and the products fractionated (Bartels-Keith, Johnson, *et al.*, *locc. cit.*). The mixed ester fractions so obtained were hydrolysed with methanolic potassium hydroxide, and the potassium phenoxyacetates which separated from the cooled reaction products were removed, washed, and converted into the corresponding acids.

Phenoxyacetic Acids from Alkoxybenzenes.—The following examples have been studied. The yields of the phenoxyacetic acids varied widely in different experiments and were considerably affected by small changes in the experimental conditions.

(i) Anisole and phenetole gave phenoxyacetic acid (4—7 and 20% respectively).

(ii) *o*-, *m*-, and *p*-Dimethoxybenzenes gave *o*-, m. p. 120—121° (up to 38%), *m*-, m. p. 116°

(up to 14%), and *p*-, m. p. 112° (up to 40%), methoxyphenoxyacetic acid respectively, which were identified by comparisons with authentic specimens.

The mixed ester fraction (2 g.) from the quinol dimethyl ether experiment was heated at 100° with 2N-hydrochloric acid (40 c.c.) and acetic acid (10 c.c.) for 5 hr. The mixture was diluted with water, and the product extracted into ether and separated into acidic, phenolic, and neutral fractions. From the acidic fraction there was obtained a little *p*-methoxyphenoxyacetic acid together with two unidentified acids, one (5 mg.) forming colourless needles, m. p. 48°, from *cyclo*hexane, and the other being a yellow phenolic oil. The main phenolic fraction gave ethyl *p*-hydroxyphenoxyacetate as colourless crystals, m. p. 120° (from dilute ethanol) not depressed on admixture with an authentic specimen (Sobotka and Austin, *J. Amer. Chem. Soc.*, 1952, **74**, 3813), and an unidentified colourless *substance*, b. p. 140° (bath-temp.)/0·1 mm., m. p. 0° (Found: C, 61·2; H, 6·1. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·2%). Treatment of the neutral oil (ethyl *p*-methoxyphenoxyacetate) with bromine gave colourless needles of *ethyl* 2 : 5-*dibromo*-4-*methoxyphenoxyacetate*, m. p. 76° (from methanol) (Found: C, 36·2; H, 3·3. $C_{11}H_{12}O_4Br_2$ requires C, 36·0; H, 3·3%). This ester was occasionally obtained in a second *form*, m. p. 95° [Found: C, 35·7; H, 3·5; *O*-Me, 16·7; Br, 44·3%; *M* (Rast), 370. $C_{11}H_{12}O_4Br_2$ requires C, 36·0; H, 3·3; 2*O*-Me, 16·85; Br, 43·8%; *M*, 368). The ultra-violet absorption spectra of these forms were identical (max. at 297 and 229 mμ; log ε 3·70 and 4·07 respectively, in ethanol), and the latter form was largely converted into the former by heating a methanolic solution under reflux. Both forms on hydrolysis gave 2 : 5-*dibromo*-4-*methoxyphenoxyacetic acid*, as prisms, m. p. 181° (from acetic acid) (Found: C, 32·1; H, 2·6. $C_9H_8O_4Br_2$ requires C, 31·8; H, 2·35%). The ultra-violet absorption spectrum of this acid in ethanolic solution showed a maximum at 298 mμ (log ε 3·70) and an inflexion at 223—229 mμ (log ε 4·13).

(iii) 1 : 2 : 4-Trimethoxybenzene gave 2 : 4-*dimethoxyphenoxyacetic acid*, m. p. 106—108°, as colourless prisms (sublimation) (Found: C, 56·7; H, 5·7. $C_{10}H_{12}O_5$ requires C, 56·6; H, 5·7%). This acid also existed in two forms, the other having m. p. 120° (see below). The lower-melting form was converted into the higher-melting after being heated at 130° for 10 min. *Ethyl* 2 : 4-*dimethoxyphenoxyacetate* had m. p. 49—50° (from aqueous ethanol) (Found: C, 60·2; H, 6·6. $C_{12}H_{16}O_5$ requires C, 60·0; H, 6·7%).

(iv) Methylenedioxybenzene gave a crude ester mixture, the main fraction of which was a yellow liquid, b. p. 101—110°/0·2 mm. This fraction (1·8 g.) was hydrolysed by adding an ice-cold solution of potassium hydroxide (1·1 g.) in methanol (10 c.c.) and subsequently heating the whole on the steam-bath for 1 hr. No potassium salt was precipitated and the solution was acidified with 10N-hydrochloric acid (1·7 c.c.) and diluted with water (30 c.c.). No acid was precipitated and the solution was extracted with ether and the ethereal extract after drying and removal of solvent yielded a brown resin which slowly crystallised. Repeated extraction of this product with hot *cyclo*hexane gave a pale yellow powder (369 mg.), and a further quantity (34 mg.) was obtained by sublimation of the residue *in vacuo*. Crystallisation from *cyclo*hexane–ether gave *benzodioxen*-2-*carboxylic acid* as colourless short needles, m. p. 116—117° (Found: C, 60·0; H, 4·5. $C_9H_8O_4$ requires C, 60·0; H, 4·5%). The ultra-violet absorption spectrum of a solution in methanol showed max. at 282 and 276 mμ (log ε 3·33 and 3·38 respectively) and min. at 280 and 243 mμ (log ε 3·31 and 1·54 respectively). A solution of the acid decolorised bromine in chloroform and potassium permanganate in acetone only very slowly. It gave no colour with concentrated sulphuric acid, and the colour test for the methylenedioxy-group with gallic acid and sulphuric acid was negative.

(v) Chroman (de Benneville and Connor, *J. Amer. Chem. Soc.*, 1940, **62**, 283) gave a chromano*cyclo*heptatrienecarboxylic acid (16%), m. p. 165—166° (from *cyclo*hexane) (Found: C, 68·7; H, 6·2. $C_{11}H_{12}O_3$ requires C, 68·7; H, 6·3%). The ultra-violet absorption spectrum of an ethanolic solution showed max. at 325 and 227 mμ (log ε 4·03 and 4·07 respectively). The acid rapidly decolorised a solution of bromine in chloroform as well as of potassium permanganate in acetone. A yellow colour was obtained with concentrated sulphuric acid.

Reaction of Anisole and Diazoacetic Ester under Ultra-violet Irradiation.—Anisole (216 g.) was mixed with diazoacetic ester (25 c.c.) and irradiated with ultra-violet light for 3 weeks. Excess of the reactants was removed from the brown mixture under reduced pressure (steam-bath), and the dark brown residue fractionated into the following: (i) b. p. 79—87°/0·01 mm. (4·4 g.), a light yellow oil giving a dark red colour with concentrated sulphuric acid; (ii) b. p. 93—120°/0·01 mm. (1·1 g.), a dark yellow oil; and (iii) residue (5·2 g.), a brown tar. Fraction (i) (1 g.) was saponified with an ice-cooled solution of potassium hydroxide (0·3 g.) in methanol (5 c.c.), and the potassium salt which precipitated was separated and dried (284 mg.). Acidification gave phenoxyacetic acid (167 mg.), m. p. 99°.

Benzodioxen-2-carboxylic Acid.—A solution of potassium hydroxide (36 g.) in water (130 c.c.) was heated with catechol (22 g.) and ethyl αβ-dibromopropionate (50 g.) in an autoclave at 145° for 1½ hr. After cooling, the dark mixture was acidified with concentrated hydrochloric acid and extracted with ether (2 × 500 c.c.). The combined ethereal solutions were extracted with saturated aqueous sodium hydrogen carbonate (3 × 150 c.c.), and the aqueous extracts again acidified and extracted with ether (2 × 200 c.c.). The solvent was removed from the dried ethereal extracts, and the dark brown solid residue crystallised from *cyclo*hexane–ether to give, after clarification with charcoal, colourless prisms of benzodioxen-2-carboxylic acid (24·1 g., 67%), m. p. 116—117° not depressed on admixture with the product obtained from methylenedioxybenzene (Found, on a sample sublimed at 0·05 mm.: C, 60·0; H, 4·7. Calc. for $C_9H_8O_4$: C, 60·0; H, 4·5%). The infra-red spectrum (Nujol mull) was identical with the product prepared from methylenedioxybenzene: max. at 1730(s), 1600, 1497(s), 1420, 1364, 1333, 1316, 1290, 1252(s), 1224(s), 1198(s), 1156, 1127(s), 1099(s), 1064(s), 1013, 939, 923, 893, 853, 833, 806, 757(s), 738, 714, and 692 cm.$^{-1}$. The ultra-violet absorption in 95% ethanol showed maxima at 282 and 276 mμ (log ε 3·33 and 3·38 respectively).

2-*Hydroxymethylbenzodioxen.*—Benzodioxen-2-carboxylic acid (1·01 g.) in dry ether (20 c.c.) was added with stirring to a cooled suspension of lithium aluminium hydride (360 mg.) in dry ether (30 c.c.). The mixture was heated under reflux for 2½ hr., cooled (ice), and decomposed with wet ether followed by water, and finally 4N-sulphuric acid. The ethereal layer was separated and the aqueous layer further extracted with ether (2 × 25 c.c.), and the combined ethereal solutions were washed with aqueous sodium hydrogen carbonate (2 × 15 c.c.), dried, and freed from solvent. The residue crystallised from ether–light petroleum (b. p. 60—80°) as colourless needles (817 mg., 88%), m. p. 85—87° raised to 89—90° after sublimation at 0·05 mm. and not depressed with an authentic specimen (J. R. Geigy, S.A., *loc. cit.*) (Found: C, 65·0; H, 6·3. Calc. for $C_9H_{10}O_3$: C, 65·05; H, 6·1%). The infra-red spectrum (Nujol mull) showed maxima at 3175(s), 2041, 1923, 1887, 1770, 1592(s), 1497(s), 1395, 1346, 1324, 1304, 1269(s), 1234, 1205(s), 1178, 1148, 1136(s), 1101(s), 1075(s), 1039(s), 1015, 961, 942(s), 925, 919, 893, 844(s), 761, 749(s), and 678 cm.$^{-1}$.

2 : 4-*Dimethoxyphenoxyacetic Acid.*—The dimethyl ether of resacetophenone (*Org. Synth.*, 1941, **21**, 103) was treated with peracetic acid, to give 2 : 4-dimethoxyphenol, b. p. 140°/15 mm., and the sodium salt of the latter treated with chloroacetic acid to give 2 : 4-*dimethoxyphenoxyacetic acid* as prisms, m. p. 120—121° (from aqueous acetone) (Found: C, 56·4; H, 5·8. $C_{10}H_{12}O_5$ requires C, 56·6; H, 5·7%).

2 : 5-*Dimethoxyphenoxyacetic Acid.*—Prepared as was the preceding acid from quinacetophenone (*Org. Synth.*, 1948, **28**, 42), the *acid* formed needles, m. p. 128—129° (Found: C, 56·3; H, 5·75%).

o-*Ethoxyphenoxyacetic acid.*—o-Hydroxyphenoxyacetic acid was ethylated with diazoethane, and the resulting ester hydrolysed with sodium carbonate solution, to give o-*ethoxyphenoxyacetic acid* as needles, m. p. 70° (from aqueous acetone) (Found, in a sample dried overnight at 40°/10 mm.: C, 56·4; H, 6·6. $C_{10}H_{12}O_4,H_2O$ requires C, 56·1; H, 6·6%). The water of crystallisation was only partly removed after sublimation *in vacuo*.

Bromination of o-*Methoxyphenoxyacetic Acid.*—The acid, m. p. 122° (1 mol.), heated with bromine (1 mol.) in chloroform, gave *ethyl 5-bromo-2-methoxyphenoxyacetate* as a colourless oil, b. p. 90° (bath-temp.)/0·01 mm. (Found: C, 45·4; H, 4·5. $C_{11}H_{13}O_4Br$ requires C, 45·6; H, 4·5%). The ester is formed by esterification of the acid with the small quantity of ethanol normally present as a stabiliser in chloroform. Alkaline hydrolysis of the ester gave the corresponding *acid*, m. p. 134°, as colourless needles after sublimation (Found: C, 41·7; H, 3·7. $C_9H_9O_4Br$ requires C, 41·4; H, 3·5%).

When *o*-methoxyphenoxyacetic acid was treated with excess of bromine in chloroform, ethyl 3(?) : 5-*dibromo-2-methoxyphenoxyacetate* was obtained as colourless prisms, m. p. 94—95° (Found: C, 36·6; H, 3·8. $C_{11}H_{12}O_4Br_2$ requires C, 36·9; H, 3·4%).

Bromination of p-*Methoxyphenoxyacetic Acid.*—Ethyl *p*-methoxyphenoxyacetate (2 g.) was heated with bromine (0·58 c.c.) in chloroform (30 c.c.) for 15 min. under reflux, and the product cooled and extracted with sodium hydrogen carbonate solution. The neutral residue, after removal of the solvent, crystallised in large prisms of ethyl 3(?)-*bromo-4-methoxyphenoxyacetate*, m. p. 44° (from methanol) (Found: C, 45·9; H, 4·9. $C_{11}H_{13}O_4Br$ requires C, 45·7; H, 4·5%). The ester was hydrolysed with 2N-sodium carbonate to the corresponding acid, m. p. 139—140°, which formed colourless needles (from aqueous acetone). Further bromination of ethyl 3(?)-bromo-4-methoxyphenoxyacetate gave ethyl 2 : 5-dibromo-4-methoxyphenoxyacetate, m. p. 76°, identical with that described above. Hydrolysis of the dibromo-ester as

before gave the corresponding acid, m. p. 181°, which on decarboxylation with soda-lime gave 2 : 5-dibromo-1 : 4-dimethoxybenzene, m. p. 144° alone and mixed with an authentic specimen obtained by bromination of quinol dimethyl ether.

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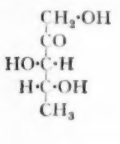
439. *The Synthesis of Sugars from Simpler Substances. Part VII.* Enzymic Synthesis of 5-Deoxy-D-Xylulose.*

By P. A. J. GORIN, L. HOUGH, and J. K. N. JONES.

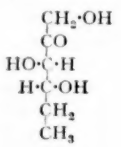
In the presence of an enzyme preparation from peas, acetaldehyde condenses with triose phosphate to give 5-deoxy-D-xylulose (I).

IT has been observed that hydroxy-aldehydes will condense with triose phosphate in the presence of an enzyme preparation from peas containing aldolase (Stumpf, *J. Biol. Chem.*, 1948, **176**, 233) to give derivatives of D-xylulose (Hough and Jones, *J.*, 1952, 4047, 4052; 1953, 342). It was of interest to determine whether the absence of hydroxyl residues in the aldehyde affects the configuration of the hydroxyl groups in the final product. Therefore, we have investigated the enzymic reaction of acetaldehyde with triose phosphate. Previous work (Meyerhof, Lohmann, and Schuster, *Biochem. Z.*, 1936, **286**, 301) had demonstrated that triose phosphate will combine with acetaldehyde in the presence of muscle aldolase to give a 5-deoxypentose phosphate. The free sugar was converted into an unidentified phenylosazone, m. p. 165—167°, thus differentiating it from 2-deoxyribose. Racker (*J. Biol. Chem.*, 1952, **196**, 347) has observed that extracts of *Bacterium coli* contain an enzyme which produces 2-deoxy-D-ribose 5-phosphate on condensation of acetaldehyde and triose phosphate.

Acetaldehyde and triose phosphate in the presence of the pea enzymes gave several substances which were separated and detected on paper chromatograms. The major product moved to the same position and produced the characteristic colour reactions on being sprayed with *p*-anisidine hydrochloride or diphenylamine–trichloroacetic acid (Hough, Jones, and Wadman, *J.*, 1950, 1702) as did authentic 5-deoxy-D-xylulose (I).



(I)



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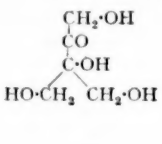

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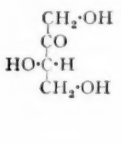
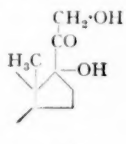


(IV)



(V)

After removal of inorganic material on ion-exchange resins the solution was concentrated and the residual syrup chromatographed on a column of cellulose (Hough, Jones, and Wadman, *J.*, 1949, 2511). The fraction of effluent containing the deoxyxylulose was collected and concentrated to a syrup which had $[\alpha]_D$ −5° (authentic 5-deoxy-D-xylulose has $[\alpha]_D$ −4°). The derived phenylosazone was indistinguishable from an authentic specimen of 5-deoxy-D-xylose phenylosazone by m. p., mixed m. p., optical rotation, and by *X*-ray diffraction analysis. It differed from 5-deoxy-L-ribose phenylosazone (prepared from L-rhamnose; Ruff, *Ber.*, 1902, **35**, 2360).

5-Deoxy-D-xylulose was prepared by isomerisation of 5-deoxy-D-xylose in pyridine and separated from unchanged aldose by chromatography on sheets of filter paper. It yielded a phenylosazone which showed the same mutarotation, m. p. and mixed m. p., and had the

* Part VI, *J.*, 1953, 1537.

same *X*-ray diffraction properties as did an authentic specimen of 5-deoxy-D-xylose phenylosazone (from 5-deoxy-D-xylose). The syrup was but slowly oxidised with sodium hypoiodite under conditions which resulted in the complete oxidation of D-xylose.

A faster-moving fraction eluted from the cellulose column contained a substance differing from 5-deoxyxylulose, but resembling 5-deoxyxylose on paper chromatograms. The optical rotation (+16°) of the syrup was similar to that of 5-deoxy-D-xylose (+13·3°) (Levene and Compton, *J. Biol. Chem.*, 1935, **111**, 325). It is possible that it was 5-deoxy-D-xylose arising from 5-deoxy-D-xylulose by isomerisation, since the enzymic reaction was carried out at pH 8.

The method of preparation of 5-deoxy-D-xylose and its phenylosazone from D-xylose (Levene and Compton, *loc. cit.*) was modified slightly in that the conversion of 1 : 2-*iso*propylidene 5-deoxy-5-iodo-D-xylose into 1 : 2-*iso*propylidene 5-deoxy-D-xylose was brought about by treatment with lithium aluminium hydride instead of by hydrogenation with Raney's nickel catalyst. This procedure, although giving the product in a lower yield, is a more convenient method.

We have observed that propaldehyde also will condense with triose phosphate in the presence of a crude enzyme preparation from peas and that the product has the properties of a 5 : 6-dideoxy-D-ketohexose. This material is very probably 5 : 6-dideoxy-D-fructose (II), but it is as yet incompletely identified. It will be of interest to see if formaldehyde will condense with triose phosphate under these conditions to give apioketose (III) and L-erythrulose (IV) (cf. Horecker and Smyrniotis, *J. Amer. Chem. Soc.*, 1953, **75**, 1009; Racker, de la Haba, and Leder, *ibid.*, p. 1110).

All the condensations of triose phosphate in the presence of the pea enzyme that we have examined have been with monofunctional and aliphatic aldehydes, and in every case have given a product with the D-xylulose configuration on $C_{(1)}$, $C_{(2)}$, $C_{(3)}$, and $C_{(4)}$. It will be of interest to determine whether aromatic aldehydes such as phloroglucinaldehyde (cf. Geissmann and Heinreimer, *Botan. Review*, 1952, **18**, 145, 165), and bifunctional aldehydes such as glyoxal, malondialdehyde, and succindialdehyde will undergo condensation with triose phosphate in the presence of the pea enzymes, especially as the last three may lead to the formation of cyclic compounds [cf. the grouping on $C_{(17)}$ of 11 : 11-dihydro-17-hydroxycorticosterone (V)].

Experimental

For details of the solvents used in chromatographic separations on paper see Hough and Jones (*J.*, 1953, 342). Optical rotations were in H_2O, determined at 20° unless otherwise stated. Microanalyses are by Mr. B. S. Noyes of Bristol. Evaporation of solutions was carried out under reduced pressure.

1 : 2-iso*Propylidene* 5-*Deoxy*-D-*xylose*.—1 : 2-*iso*Propylidene 5-deoxy-5-iodo-D-xylose (Levene and Compton, *loc. cit.*) (9·2 g.) in dry ether (20 c.c.) was added slowly with stirring to an excess of lithium aluminium hydride (2 g.) suspended in dry ether (50 c.c.). After 30 min.' stirring, water (5 c.c.) was added dropwise to decompose excess of the reagent. Insoluble material was filtered off, and the filtrate evaporated to a small volume and a chloroform–water mixture (200 c.c.; 1 : 1) was then added. After separation of the chloroform layer, the aqueous layer was extracted with chloroform (2 × 100 c.c.). The combined extracts were dried ($MgSO_4$), filtered, and evaporated to a syrup. The syrup was crystallised from ether–light petroleum (b. p. 40—60°), to yield 1 : 2-*iso*propylidene 5-deoxy-D-xylose (3·7 g.), m. p. 68—69°, $[\alpha]_D$ −20° ± 2° (*c*, 3·0) (Found: C, 55·2; H, 7·7. Calc. for $C_8H_{14}O_4$: C, 55·2; H, 8·0%). This product was used for preparation of 5-deoxy-D-xylose and its phenylosazone.

5-*Deoxy*-D-*xylulose from* 5-*Deoxy*-D-*xylose*.—5-Deoxy-D-xylose (0·9 g.) was heated at 100° for 20 hr. in dry pyridine (20 c.c.). The solution was evaporated to a syrup. Chromatographic examination of the product showed that it contained, as well as 5-deoxy-D-xylose, a slower-moving substance which gave colour reactions (*p*-anisidine hydrochloride and diphenylamine–trichloroacetic acid sprays) which differed from those of 5-deoxy-D-xylose. This substance was separated from 5-deoxy-D-xylose by chromatography on several large sheets of filter paper (Flood, Hirst, and Jones, *Nature*, 1947, **160**, 86) with butanol–ethanol–water (40 : 11 : 19 v/v). The syrupy product had $[\alpha]_D$ −4° ± 1°.

Hypoiodite Oxidation of 5-*Deoxy*-D-*xylulose*.—Treatment of the syrup (2·19 mg.) with sodium hypoiodite (18 hr.) under conditions specified by Chanda, Hirst, Jones, and Percival (*J.*, 1950,

1289) resulted in 26% of it being oxidised. A similar determination on D-xylose resulted in 96% oxidation.

5-Deoxy-D-xylose Phenylosazone from 5-Deoxy-D-xylulose.—The syrup (113 mg.) was warmed at 50° for 18 hr. in aqueous phenylhydrazine acetate. On cooling, the yellow product was filtered off, washed with water, then with benzene, and finally recrystallised from aqueous methanol. The product (56 mg.) (Found: C, 65·2; H, 6·25; N, 18·1. Calc. for $C_{17}H_{20}O_2N_4$: C, 65·4; H, 6·4; N, 17·9%), $[\alpha]_D$ 67° → 0° (±7°) (*c*, 0·6 in pyridine–ethanol, 3 : 2 v/v) had m. p. 174—175°, undepressed on admixture with authentic 5-deoxy-D-xylose phenylosazone. It gave an *X*-ray diffraction pattern identical with authentic material prepared from 5-deoxy-D-xylose.

Condensation of Acetaldehyde with Triose Phosphate.—The sodium salt of hexose diphosphate (10 g.) was dissolved in water (500 c.c.) and the pH brought to 8 by the addition of 0·1N-sodium hydroxide. A solution of aldolase (200 c.c.) prepared from pea seeds (100 g.) by Stumpf's method (*loc. cit.*) was added. Redistilled acetaldehyde (4 c.c.) in water (100 c.c.) was then added drop-wise during an hour. The solution was incubated in a tightly stoppered flask at 37° for 4 days. Protein was then coagulated by heating the solution at 90° (1 hr.). The cooled solution was filtered, and the filtrate evaporated to 500 c.c. and deionised by successive passages through columns of Amberlite resins IR-120 and IR-4B. The effluent was concentrated to a syrup (5 c.c.) which was extracted with methanol. The methanolic solution was filtered and concentrated to a syrup, which was transferred to a column of cellulose (Hough, Jones, and Wadman, *loc. cit.*) and fractionated. Benzene–ethanol–water (30 : 10 : 3 v/v; top layer) (500 c.c.) was first passed down the column, followed by butanol. The effluent was collected on an automatic fraction cutter, and the fractions were examined chromatographically (solvent butanol–ethanol–water, 40 : 11 : 19 v/v). The sugars were detected after spraying the paper with ammoniacal silver nitrate and heating it. The presence of four substances which had rates of movement relative to rhamnose (1·0) of 2·4, 1·9, 1·73, and 1·53 was observed. One sugar moved at the rate of 5-deoxy-D-xylulose (1·53) and a second at the rate of 5-deoxy-D-xylose (1·73). The appropriate fractions which contained these sugars were collected and concentrated. The sugar which moved at the rate of 5-deoxy-D-xylulose also resembled it in that it gave a yellow colour with the *p*-anisidine spray and a pale green colour with the diphenylamine–trichloroacetic acid spray, while the sugar which resembled 5-deoxy-D-xylose gave an orange colour with the *p*-anisidine spray and a blue-green colour with the other reagent.

5-Deoxy-D-xylulose prepared by Enzymic Reaction.—This fraction, a syrup (A) (149 mg.), showed $[\alpha]_D$ −5° ± 1° (*c*, 1·49 in MeOH), whereas authentic 5-deoxy-D-xylulose has $[\alpha]_D$ −4° ± 1° (*c*, 1·1 in MeOH). When the sugar (A) (140 mg.) was dissolved in aqueous phenylhydrazine acetate and left for 18 hr. at 35°, a crystalline phenylosazone separated. It was collected on a filter, washed with water and with benzene, and dried. The product (61 mg.) was recrystallised from methanol–water and had $[\alpha]_D$ +74° → + 7° (±7°) (*c*, 0·6 in pyridine–ethanol, 3 : 2 v/v), m. p. 174—175°, not depressed on admixture with an authentic specimen (Found: C, 65·3; H, 6·3; N, 17·9. Calc. for $C_{17}H_{20}O_2N_4$: C, 65·4; H, 6·4; N, 17·9%). Meyerhof, Lohmann, and Schuster (*loc. cit.*) record m. p. 165—167°. The phenylosazone gave an *X*-ray diffraction pattern identical with that given by an authentic specimen (Levene and Compton, *loc. cit.*) and differed from that of 5-deoxy-L-ribose phenylosazone {$[\alpha]_D$ + 60° → 74° ± 7° (*c*, 0·6 in pyridine–ethanol, 3 : 2 v/v)} prepared from L-rhamnose (Ruff, *loc. cit.*).

5-Deoxy-D-xylose prepared by Enzymic Reaction.—This fraction (51 mg.) showed $[\alpha]_D$ +16°. 5-Deoxy-D-xylose has $[\alpha]_D^{24}$ +13·3° (Levene and Compton, *loc. cit.*). Neither a crystalline phenylosazone nor a crystalline *iso*propylidene derivative (Levene and Compton, *loc. cit.*) could be prepared from it. Although its behaviour on paper chromatograms was identical with that of 5-deoxy-D-xylose, conclusive evidence of its identity was not obtained.

The authors thank Mr. D. A. Brown for determining the *X*-ray diffraction patterns, the Chemical Society for a grant and the City of Bristol Education Authorities for a Scholarship (to P. A. J. G.).

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440. *Aromatic Azo-compounds. Part I. Oxidation of* cis- *and* trans-*Azobenzene.*

By G. M. Badger, R. G. Buttery, and G. E. Lewis.

The oxidation of *cis*-azobenzene with perbenzoic acid has given *cis*-azoxybenzene; *cis*-azoxy-compounds have also been obtained by oxidation of *cis-m*-azotoluene and *cis-p*-azotoluene. Reduction of *cis*-azoxybenzene with lithium aluminium hydride, however, gave *trans*-azobenzene. *trans*-Azobenzene gave *trans*-azoxybenzene on oxidation in the dark, but some *cis*-azoxybenzene was obtained on oxidation in sunlight.

A method has been developed for studying the rates of reaction of azo-compounds with perbenzoic acid, and *cis*-azobenzene has been shown to react very much more rapidly than the *trans*-compound. The results indicate that the electron density at the azo-linkage in *cis*-azobenzene is much greater than that in the *trans*-isomer.

The aromatic azo-compounds are of considerable importance, particularly in connection with the study of the relationship between chemical constitution and colour. Many useful dyes belong to this class, and some azo-compounds have proved to be of medicinal value. In addition, certain aminoazo-compounds have been shown to produce liver tumours when administered for long periods to experimental animals. *o*-Aminoazotoluene and 4-dimethylaminoazobenzene behave in this way, and although numerous related compounds are known to be liver carcinogens, a relatively specific structure seems to be required (Badger and Lewis, *Brit. J. Cancer*, 1952, in the press). Pullman (*Compt. rend.*, 1946, **222**, 1501; 1947, **224**, 1773; Pullman and Pullman, *Rev. Sci.*, 1946, **84**, 145) has suggested that carcinogenic activity is associated with an optimum density of electrons at the azo-linkage (called the *K'* region) and that the magnitude of the charge is governed by the substituents present. It seemed of interest to examine this hypothesis experimentally, and the work reported in the present series of papers was undertaken to this end.

Other things being equal, the greater the electron density at the nitrogen atoms, the greater the reactivity towards electrophilic reagents. It therefore seemed that a suitable method would be to study the rate of addition of an electrophilic reagent to the *K'* region in a series of carcinogenic and related non-carcinogenic azo-compounds. The per-acids are known to be electrophilic reagents (Swern, *J. Amer. Chem. Soc.*, 1947, **69**, 1692; *Chem. Reviews*, 1949, **45**, 1; Derbyshire and Waters, *Nature*, 1950, **165**, 401), and a method for the determination of the rate of reaction of azo-compounds with perbenzoic acid has accordingly been developed (for a preliminary account of some of this work, see Badger and Lewis, *ibid*, 1951, **167**, 403).

Boëseken and Stuurman (*Rec. Trav. chim.*, 1937, **56**, 1034) studied the rate of oxidation of various ethylenic compounds with peracetic acid, and the experimental procedure now used was based on their method. The reactions were carried out in benzene solution, at constant temperature, perbenzoic acid being used. Aliquot portions of reaction mixture were removed at suitable intervals, and the residual perbenzoic acid estimated by titrating the iodine liberated from acidified potassium iodide solution with standard sodium thiosulphate solution.

Much higher reaction rates were obtained when using samples of perbenzoic acid which had undergone an appreciable degree of spontaneous decomposition. This was interpreted as a catalytic effect caused by the presence of benzoic acid, and it was confirmed by studying the rate of oxidation of azobenzene with a mixture containing equimolecular proportions of benzoic and perbenzoic acids, a significant increase in the rate of reaction being observed. A similar catalytic effect of benzoic acid has already been noted by Friess (*J. Amer. Chem. Soc.*, 1949, **71**, 2571). For this reason, only freshly prepared solutions of perbenzoic acid were used for all rate determinations.

The rate of reaction was also increased when the reaction mixtures were exposed to the ordinary light. Reproducible results could only be obtained when the reactions were carried out in flasks which had been well covered with a black enamel.

trans-Azobenzene is known to be converted into an equilibrium mixture of *cis*- and *trans*-azobenzene by light, and it is likely that the catalytic effect of light in the perbenzoic acid oxidation might be associated with this fact, since *cis*-azobenzene reacts very much more rapidly than the *trans*-azo-compound (see below).

The oxidation of *trans*-azobenzene was carried out at four different temperatures, and in each case at least three runs were made with wide variations in the $(a - b)$ factor. The reactions were followed to at least 50% completion, and the results (Tables 1, 2, and 3) indicate that the reaction is of the second order. *cis*-Azobenzene has also been studied at four temperatures, in the dark, and the rate constants are included in Table 2. *cis*-Azobenzene is slowly transformed into the stable *trans*-form; it has been shown, however, that the half-life of the *cis*⟶*trans*-transformation in the dark is 119 hr. at 25° (Hartley, *J.*, 1938, 633), and as the oxidation proceeds very rapidly, this transformation cannot have an appreciable effect.

TABLE 1. *Reaction between* trans-*azobenzene and perbenzoic acid in benzene solution at* 25°.

$(a - b)$, mole/l.	0·00158	0·00335	0·01812
10^3k_2, mole^{-1} min.$^{-1}$ l.	13·8 ± 0·3	14·1 ± 0·2	13·9 ± 0·3
		Mean :	13·9 ± 0·3

TABLE 2. *Rate constants and activation energies for reaction between* cis- *and* trans-*azobenzene and perbenzoic acid.**

	10^3k_2 (mole^{-1} min.$^{-1}$ l.)				ΔH			
Azobenzene	15°	20°	25°	30°	(kcal.)	*X*	*Y*	*Z*
trans-	5·80 ± 0·07	9·02 ± 0·15	13·9 ± 0·03	20·9 ± 0·03	14·8 ± 0·3	0	0	0
cis-	374 ± 6	527 ± 9	749 ± 11	1085 ± 25	12·3 ± 0·5	−2·5	−0·1	−2·4

* ΔH_0, ΔS_0, and ΔF_0 are the heat of activation, the entropy of activation, and the free energy of activation, respectively, for *trans*-azobenzene. $X = \Delta H^{\ddagger} - \Delta H_0^{\ddagger}$; $Y = T(\Delta S^{\ddagger} - \Delta S_0^{\ddagger})$; $Z = \Delta F^{\ddagger} - \Delta F_0^{\ddagger}$; all in kcal. The quantities $T(\Delta S^{\ddagger} - \Delta S_0^{\ddagger})$ and $\Delta F^{\ddagger} - \Delta F_0^{\ddagger}$ are calculated from the data at 25°.

trans-Azoxybenzene was isolated in almost quantitative yield from the products of oxidation of *trans*-azobenzene with perbenzoic acid in the dark, and the reaction may therefore be represented by the equation :

$$\mathrm{Ar{-}\overset{\cdot\cdot}{N}{=}\overset{\cdot\cdot}{N}{-}Ar' + Ph{\cdot}CO_3H = Ar{-}\overset{\cdot\cdot}{\underset{\downarrow}{N}}{=}\overset{\cdot\cdot}{N}{-}Ar' + Ph{\cdot}CO_2H}$$
$$\mathrm{O}$$

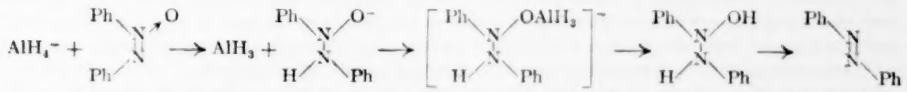
cis-Azoxybenzene is rapidly converted into the more stable *trans*-form, especially in sunlight and at high temperatures : it may be noted that Cook and Jones (*J.*, 1941, 184) isolated only *trans*-azoxybenzene from the oxidation of *cis*-azobenzene with peracetic acid. *cis*-Azoxybenzene has now been isolated, however, following oxidation of *cis*-azobenzene with perbenzoic acid. The oxidation was carried out at room temperature in the dark, concentrations being such as to enable the reaction to proceed almost to completion within 3 hr. Even under these conditions, some *trans*-azoxybenzene was also isolated. *cis*-Azoxybenzene has also been isolated from the products of oxidation of excess of *trans*-azobenzene with a concentrated solution of perbenzoic acid, in sunlight; and this confirms the interpretation, given above, for the catalytic effect of light in this reaction.

The method has also been extended to two other compounds, and in qualitative experiments, *cis*-azoxy-compounds have been produced by oxidation of *cis*-*m*- and of *cis*-*p*-azotoluene with perbenzoic acid.

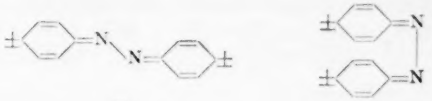
Although there was no doubt as to the structures of these compounds (Hartley and Le Fèvre, *J.*, 1939, 531; Calderbank and Le Fèvre, *J.*, 1948, 1949), this seems to be the first time that the *cis*-azo-compounds have been directly related to the *cis*-azoxy-compounds.

trans-Azoxybenzene is known to give *trans*-azobenzene on reduction (Nystrom and Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 3738), and the inter-relationship would be completed if *cis*-azoxybenzene could be reduced to *cis*-azobenzene. It has been found, however, that reduction of *cis*-azoxybenzene with lithium aluminium hydride yields only *trans*-azobenzene. This result is of some importance, as it suggests that the reduction must proceed *via* an intermediate having a single bond between the nitrogen atoms. Such an intermediate

would have free rotation about this bond, and the more stable *trans*-form of the azo-compound would naturally be formed. By analogy with the postulated mechanism for the reduction of epoxides with lithium aluminium hydride (Brown, *Org. Reactions*, 1951, **6**, 469), it is suggested that the aluminohydride ion adds to the azoxy-compound, and that subsequent decomposition gives the *trans*-azo-compound in accordance with the following scheme :



Discussion.—The structures and molecular dimensions of both the *cis*- and the *trans*-form of azobenzene have been determined by quantitative *X*-ray investigation (de Lange, Robertson, and Woodward, *Proc. Roy. Soc.*, 1939, *A*, **171**, 398; Robertson, *J.*, 1939, 232; Hampson and Robertson, *J.*, 1941, 409). The *trans*-azobenzene molecule is very nearly coplanar. The N=N bond is 1·23 Å long, and the C–N bonds 1·41 Å. As the normal C–N single-bond distance is 1·47 Å, and the normal C=N double-bond distance 1·28 Å, structures such as (I) must make a considerable contribution to the normal state of the molecule. The N=N bond must therefore have some single-bond character and the C–N bonds some double-bond character. According to Buu-Hoï *et al.* (*Bull. Soc. chim.*, 1951, **18**, 132c), the N=N bond has a bond order of 1·746, and the C–N bonds an order of 1·470. In addition, the two nitrogen " lone pairs " must also be shared to some extent with the ring systems, and the net result is that the electron density around the N=N linkage must be considerably below the value expected in the absence of such conjugation.



(I) (II)

The *cis*-azobenzene molecule, on the other hand, is not coplanar. Owing to steric effects, the two benzene rings are rotated about 50° from the planar positions. The N=N bond is 1·23 Å long and the C–N bonds were found to be 1·46 Å, almost identical with the length of normal C–N single bonds. The departure from coplanarity has therefore led to a suppression of conjugation, and structures such as (II) cannot contribute significantly to the resonance hybrid. The net result must be that the electron density around the N=N linkage in *cis*-azobenzene is much greater than that in the *trans*-compound.

On oxidation with perbenzoic acid, both azobenzenes are converted into the azoxy-compounds. The N–O bond is known to be of the co-ordinate covalent type, and an essential feature of the reaction must therefore be the localisation of two electrons at one of the nitrogen atoms. It is reasonable to suppose that the energy required to bring about this localisation will be a major part of the activation energy for the reaction. Furthermore, other things being equal, the greater the initial electron density on the nitrogen atom, the less the energy required to localised the two electrons.

The results summarised in Table 2 indicate that *cis*-azobenzene is oxidised very much more rapidly than the *trans*-compound. The entropies of activation ($\Delta S^{\ddagger}$) are essentially the same, and the heat of activation ($\Delta H^{\ddagger}$) and the free energy of activation ($\Delta F^{\ddagger}$) are significantly smaller in the case of *cis*-azobenzene. It may be concluded, therefore, that the oxidation results confirm the greater electron density and electron availability at the N=N linkage in the *cis*-compound.

Experimental

Materials.—" AnalaR " benzene was used in all kinetic experiments. Perbenzoic acid was prepared by Brooks and Brooks's method (*J. Amer. Chem. Soc.*, 1933, **55**, 4309) except that " AnalaR " benzene was used instead of chloroform to extract the per-acid. Fresh perbenzoic acid was prepared for each series of determinations, and when not in use the solution was kept in the refrigerator. After several recrystallisations from alcohol, commercial *trans*-azobenzene had m. p. 68°. It was further purified chromatographically by adsorption on

alumina from light petroleum solution and elution with light petroleum–benzene. No bands due to impurities were obtained. After a further recrystallisation from alcohol, *trans*-azobenzene, m. p. 68°, was obtained, and this was used in all the kinetic experiments. *cis*-Azobenzene was prepared according to Hartley (*J.*, 1938, 633); after recrystallisation from light petroleum (b. p. <45°) it had m. p. 71°.

Reaction.—The accurately weighed azo-compound (0·5, 0·75, or 1·0 × 10^{-3} mole) was dissolved in "AnalaR" benzene in a standard flask (25·0 or 50·0 ml.) well covered with black enamel, and the flask placed in the thermostat. The stock solution of freshly prepared 0·5—0·7N-perbenzoic acid was also placed in the thermostat, and when equilibrium had been attained, 5·00 ml. were added to the solution of azo-compound, with gentle mixing. The time of half-addition was taken as zero time. The solution was quickly made up to the mark with "AnalaR" benzene at the temperature of the reaction, and the mixture vigorously shaken. An aliquot portion was then quickly removed, and the perbenzoic acid concentration estimated by titration of the iodine liberated from acidified potassium iodide against standard sodium thiosulphate. Further aliquots were removed at suitable time intervals, the time for each reading being taken at the instant of the addition and mixing with the potassium iodide solution. As a rule, the first reading was taken 3—4 min. after zero time, and the initial concentration of per-acid was therefore determined by extrapolation of the plot of the remaining per-acid concentration against the time. The reaction was followed to at least 50% of completion, and second-order rate constants were calculated.

Table 3 records the results obtained in a typical run with *trans*-azobenzene. In this experiment, 1·0 × 10^{-3} mole of azobenzene was used in a reaction mixture totalling 25·0 ml. 2·0-ml. samples were withdrawn at intervals and titrated with N/40-sodium thiosulphate; k_2 is given in $mole^{-1}$ $min.^{-1}$ l.

TABLE 3. *Typical run with* trans-*azobenzene, at* 25°.

Time, min. ...	0	3	31	108	227	362	495	1358	1676	2090	3030
Titre, ml. ...	(9·30) *	9·29	9·14	8·77	8·28	7·81	7·40	5·73	5·30	4·83	4·29
10^3k_2	—	—	13·94	14·24	13·94	13·80	13·79	13·49	13·78	14·35	13·73

Mean 13·90 ±

* By extrapolation.

trans-*Azoxybenzene.*—When the reaction with *trans*-azobenzene was virtually complete, the reaction mixture was washed with dilute sodium carbonate solution, and then with water, and dried. After evaporation of the solvent, the product was purified by chromatography on alumina from light petroleum solution. It was identified as *trans*-azoxybenzene, m. p. 36°, by direct comparison with an authentic specimen.

cis-*Azoxybenzene.*—(i) *cis*-Azobenzene (1·5 g.) was added to a 0·78N-solution of perbenzoic acid in chloroform (50 c.c.), and oxidation allowed to proceed in the dark at room temperature (26°) for 2½ hr. After being washed with 5% sodium hydroxide solution (3 × 40 c.c.) and then with water (50 c.c.), the chloroform solution was quickly dried (Na_2SO_4) and evaporated at room temperature under reduced pressure. The resulting yellow solid was freed from *trans*-azoxybenzene by trituration with light petroleum (b.p. 40—60°; 3 × 20 c.c.) and then had m. p. 84° (yield 0·75 g.). Pure *cis*-azoxybenzene, m. p. 87°, was obtained by further trituration with light petroleum (3 × 20 c.c.) and was identified by direct comparison with a specimen prepared according to Müller and Kreutzmann (*Annalen*, 1932, **495**, 132). Its identity was also confirmed by its conversion into *trans*-azoxybenzene, m. p. 36°, by heating at 100° for ½ hr.

(ii) *trans*-Azobenzene (2·0 g.) was added to a 1·5N-solution of perbenzoic acid in chloroform (30 c.c.), and the resulting solution exposed to sunlight. The flask was cooled by immersion in a beaker of water. After 2 hr., the solution was washed with 10% sodium carbonate solution and dried, and the chloroform evaporated at room temperature. The crude solid remaining was freed from excess of azobenzene and from *trans*-azoxybenzene by washing it with light petroleum (b. p. 40—60°, 5 × 30 c.c.); the resulting *cis*-azoxybenzene (0·3 g.) had m. p. 86°. On being heated at 100° for ½ hr., it was converted into *trans*-azoxybenzene, m. p. 36°.

cis-m-*Azoxytoluene.*—*cis-m*-Azotoluene has been reported as a red oil (Cook and Jones, *J.*, 1939, 1309). In the present work, it was prepared by the method used for *cis*-azobenzene (Hartley, *loc. cit.*) and purified by chromatography. The product solidified on storage at −5° and after recrystallisation from light petroleum had m. p. 46°. By the same procedure as above, it gave *cis-m*-azoxytoluene, m. p. 87° on oxidation with perbenzoic acid (Müller and Kreutzmann, *loc. cit.*, give m. p. 89°). When heated at 100° for 1 hr., it was converted into *trans-m*-azoxytoluene, m. p. 37°.

cis-p-*Azoxytoluene.*—*cis-p*-Azotoluene was prepared according to Cook's method (*J.*, **1938**, 876). It gave *cis-p*-azoxytoluene, m. p. 84°, on oxidation with perbenzoic acid (Müller and Kreutzmann, *loc. cit.*, give m. p. 83—85°). When heated at 100° for 1 hr., it was converted into *trans-p*-azoxytoluene, m. p. 74°.

Reduction of cis-*Azoxybenzene with Lithium Aluminium Hydride.*—A solution of *cis*-azoxybenzene (0·22 g.) in anhydrous ether (20 c.c.) was added dropwise to lithium aluminium hydride (0·3 g.) in ether (15 c.c.) at room temperature. After 1 hr., water (5 c.c.) was added gradually, the reaction mixture filtered, and the ether evaporated. The resulting solid was purified chromatographically by adsorption on alumina from light petroleum. Only one band was obtained. This was washed through, and the solvent evaporated. The *trans*-azobenzene obtained (0·06 g.) had m. p. 68°, unchanged after resolidification.

This work was carried out during the tenure by one of us (G. E. L.) of a C.S.I.R.O. scholarship, for which we express our thanks.

UNIVERSITY OF ADELAIDE. [*Received, January 14th*, 1953.]

441. *Aromatic Azo-compounds. Part II.* Oxidation of Substituted Azobenzenes.*

By G. M. BADGER and G. E. LEWIS.

The rates of oxidation of various substituted azobenzenes with perbenzoic acid have been determined at three temperatures, and the energies of activation calculated. All *meta*- and *para*-substituted compounds are found to have the same entropy of activation. Electron-releasing substituents decrease, and electron-attracting substituents increase, the heat of activation and free energy of activation. The effects of two substituents appear to be accurately additive, and there is a linear relationship between the rate constants and the Hammett " sigma " constants for the various substituents.

MANY derivatives of azobenzene produce cancer of the liver when administered to rats and mice (for review, see Badger and Lewis, *Brit. J. Cancer*, 1952, in the press). Most of the active compounds are 4-amino-, 4-methylamino-, or 4-dimethylamino-derivatives, but additional substituents have a profound effect on the relative potency of the resulting compound. For example, 4-dimethylamino-4'-methylazobenzene is much less active than 4-dimethylaminoazobenzene, but 4-dimethylamino-4'-fluoroazobenzene is rather more active than the parent base. More than thirty substituted 4-dimethylaminoazobenzenes have been tested for carcinogenic activity; some are more active than the parent base, some less active, and several entirely inactive. The relationship between chemical constitution and carcinogenic activity has not been extensively studied, but Pullman (*Compt. rend.*, **1946**, **222**, **1501**) has suggested that the electron density at the azo-linkage is an important factor.

It has not been possible to examine the rate of oxidation of 4-dimethylaminoazobenzene with perbenzoic acid as reaction occurs far too rapidly. However, the effect of many other substituents on the electron density around the azo-nitrogen atoms has been examined by determining the rates of oxidation of various substituted azobenzenes.

The oxidations were carried out, at three temperatures, by the method given in the preceding paper, and the results are summarised in the Table. For every compound, the logarithms of the three rate constants fell very nearly on a straight line when plotted against the reciprocal of the absolute temperature, and the heat of activation ($\Delta H^{\ddagger}$) has been calculated in each case. The difference in the heat of activation relative to azobenzene itself ($\Delta H^{\ddagger} - \Delta H_0^{\ddagger}$) has also been evaluated. The difference of the free energy of activation relative to azobenzene ($\Delta F^{\ddagger} - \Delta F_0^{\ddagger}$) has been calculated from the rate constants at 25° for the compound in question and that for azobenzene. In addition, the difference in the entropy of activation relative to azobenzene ($\Delta S^{\ddagger} - \Delta S_0^{\ddagger}$) has been evaluated from the PZ factors at 25° and multiplied by the absolute temperature.

The probable error for $\Delta F^{\ddagger} - \Delta F_0^{\ddagger}$ must be very small, but that for $\Delta H^{\ddagger} - \Delta H_0^{\ddagger}$ and for $T(\Delta S^{\ddagger} - \Delta S_0^{\ddagger})$ is in the region of $\pm 0{\cdot}5$ kcal. Within experimental error, therefore,

* Part I, preceding paper.

and with the exception of 2 : 2′-dimethylazobenzene (the only *ortho*-substituted derivative examined) it is found that the entropy of activation remains constant for all the substituted azobenzenes examined. This is indicated by the fact that $T(\Delta S^{\ddagger} - \Delta S_0^{\ddagger}) \approx 0$ in each case, and that there is a linear relationship between the heat of activation and the

*Rate constants and activation energies for reaction between substituted azo-compounds and perbenzoic acid.**

No.	Substituted azobenzene	$10^3 k_2$ (mole^{-1} min.$^{-1}$ l.) 15°	25°	30°	$\Delta H^{\ddagger}$ (kcal.)	X	Y	Z
1.	4 : 4′-Dimethoxy-	80·1 ± 2·9	179 ± 7	255 ± 6	13·4 ± 0·7	−1·4	+0·1	−1·5
2.	4-Methoxy-	25·4 ± 0·4	58·2 ± 1·8	83·3 ± 2·0	13·7 ± 0·5	−1·1	−0·2	−0·8
3.	4 : 4′-Dimethyl-	21·4 ± 0·4	49·1 ± 1·6	71·6 ± 2·1	14·0 ± 0·6	−0·8	−0·1	−0·7
4.	4-Methyl-	12·0 ± 0·2	28·2 ± 0·8	41·7 ± 1·1	14·4 ± 0·5	−0·4	0	−0·4
5.	3 : 3′-Dimethyl-	10·1 ± 0·2	23·9 ± 0·6	34·7 ± 0·7	14·3 ± 0·5	−0·5	−0·2	−0·3
6.	3-Methyl-	7·20 ± 0·09	17·1 ± 0·4	25·3 ± 0·4	14·5 ± 0·3	−0·3	−0·2	−0·1
7.	3-Methoxy-	5·81 ± 0·08	14·4 ± 0·4	21·6 ± 0·4	15·2 ± 0·4	+0·4	+0·4	0
8.	Parent substance	5·80 ± 0·07	13·9 ± 0·3	20·9 ± 0·3	14·8 ± 0·3	0	0	0
9.	4-Fluoro-	3·99 ± 0·08	9·73 ± 0·17	14·6 ± 0·4	15·0 ± 0·6	+0·2	0	+0·2
10.	4-Chloro-	3·07 ± 0·07	7·54 ± 0·12	11·5 ± 0·2	15·3 ± 0·5	+0·5	+0·1	+0·4
11.	4-Bromo-	2·92 ± 0·05	7·09 ± 0·15	11·0 ± 0·2	15·3 ± 0·4	+0·5	+0·1	+0·4
12.	3-Carbethoxy-	2·29 ± 0·05	5·65 ± 0·18	8·61 ± 0·17	15·3 ± 0·5	+0·5	0	+0·5
13.	4-Carbethoxy-	2·03 ± 0·04	5·03 ± 0·14	7·54 ± 0·13	15·2 ± 0·4	+0·4	−0·2	+0·6
14.	3-Bromo-	1·73 ± 0·04	4·51 ± 0·12	6·82 ± 0·13	15·9 ± 0·5	+1·1	+0·4	+0·7
15.	4 : 4′-Dichloro-	1·71 ± 0·03	4·38 ± 0·14	6·76 ± 0·11	15·9 ± 0·4	+1·1	+0·4	+0·7
16.	2 : 2′-Dimethyl-	1·70 ± 0·03	4·36 ± 0·13	6·88 ± 0·14	16·2 ± 0·5	+1·4	+0·7	+0·7
17.	3-Chloro-	1·69 ± 0·03	4·33 ± 0·10	6·58 ± 0·11	15·7 ± 0·4	+0·9	+0·2	+0·7
18.	4 : 4′-Dibromo-	1·64 ± 0·03	4·10 ± 0·15	6·49 ± 0·12	15·9 ± 0·4	+1·1	+0·4	+0·7
19.	3-Fluoro-	1·66 ± 0·03	4·06 ± 0·12	6·34 ± 0·12	15·5 ± 0·4	+0·7	0	+0·7
20.	3-Nitro-	0·767 ± 0·015	2·05 ± 0·09	3·13 ± 0·09	16·3 ± 0·6	+1·5	+0·3	+1·1
21.	3 : 3′-Dichloro-	0·559 ± 0·014	1·45 ± 0·06	2·24 ± 0·07	16·0 ± 0·7	+1·2	−0·1	+1·3
22.	4-Nitro-	0·158 ± 0·005	0·416 ± 0·021	0·681 ± 0·022	16·9 ± 0·7	+2·1	0	+2·1

* $X = \Delta H^{\ddagger} - \Delta H_0^{\ddagger}$; $Y = T(\Delta S^{\ddagger} - \Delta S_0^{\ddagger})$; $Z = \Delta F^{\ddagger} - \Delta F_0^{\ddagger}$; all in kcal.

logarithm of the rate constant at 25° (Fig. 1). All the points fall about the line of gradient $-2{\cdot}303\boldsymbol{R}T$ which is drawn through the point for azobenzene. The point for 2 : 2′-dimethylazobenzene shows the greatest displacement from the line.

As the entropy of activation is essentially constant for all *meta*- and *para*-substituted azobenzenes, then $\Delta H^{\ddagger} - \Delta H_0^{\ddagger} = \Delta F^{\ddagger} - \Delta F_0^{\ddagger}$, and either $\Delta H^{\ddagger}$ or $\Delta F^{\ddagger}$ may be used as an index of relative electron density or electron availability at the reacting centre (cf. Hammett, " Physical Organic Chemistry," McGraw-Hill, 1940, pp. 118 *et seq.*). In the Table, the various compounds have been arranged in order of decreasing electron density around the azo-nitrogen atoms; but clearly, it is impossible accurately to distinguish between compounds showing only small differences in rate constants.

Examination of the Table shows that the various substituents affect the heat of activation and the free energy of activation (and hence the electron density at the azo-nitrogen atoms) more or less as expected. Electron-releasing substituents decrease the energy of activation and increase the rate of reaction, and electron-attracting substituents have the reverse effects. The results for 3-methyl- and 3 : 3′-dimethyl-azobenzenes, for example, indicate that a *meta*-methyl group does act slightly as an electron-donor to the azo-nitrogen atoms. Similarly, the results for 4-methyl- and 4 : 4′-dimethyl-azobenzenes indicate that a *para*-methyl group produces a much greater increase in electron density at the reacting centre. On the other hand, the halogens produce a decrease in the electron density. The effect was found to be relatively small when the halogen substituent was in the *para*-position, for in these circumstances the $-I$ effects of the substituents are largely counterbalanced by the $+M$ effects. When the halogen substituent was present in the *meta*-position, its effect was much greater. Incidentally, it was not possible to examine iodoazobenzenes in this reaction, as the perbenzoic acid also attacked the iodo-substituent.

Further examination of the effects of the various substituents shows that there is a linear relationship between the logarithm of the rate constant (at 25°) and Hammett's " sigma " constant for the substituent (Hammett, *op. cit.*, pp. 184 *et seq.*). This is shown in Fig. 2, and as some of the sigma constants are not known very accurately, the

relationship must be considered very satisfactory. In some cases the probable error in the sigma constant is of the order of 0·1, and this no doubt accounts for one or two apparent anomalies. For example, the free energy of activation for 3-methoxyazobenzene (see Table) was found to be the same as that for azobenzene, in spite of the fact that Hammett gives a 3-methoxy-group a sigma constant of +0·115. This value would suggest that $\Delta F^{\ddagger} - \Delta F_0^{\ddagger}$ should be about +0·3 kcal., and that the reaction rate for 3-methoxyazobenzene should be between those for the 4-fluoro- and the 4-chloro-derivative. However, the probable error in the sigma constant for this substituent is 0·102, and it may well be that the true value for a *m*-methoxy-substituent is close to zero. Hammett gives two values for a *p*-nitro-group and it is difficult to choose which is the more satisfactory for the present comparison. Both values have therefore been included in Fig. 2.

The effects of two substituents in the *meta*- and *para*-positions appear to be accurately additive. This is shown by the fact that the $\Delta F^{\ddagger} - \Delta F_0^{\ddagger}$ values for disubstituted compounds are almost identical with the sum of the $\Delta F^{\ddagger} - \Delta F_0^{\ddagger}$ values for the corresponding mono-substituted compounds. It is also confirmed by the fact that the rate

FIG. 1.

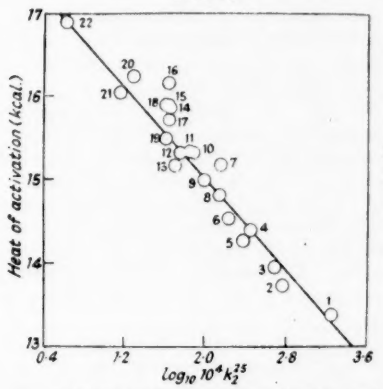


FIG. 2.

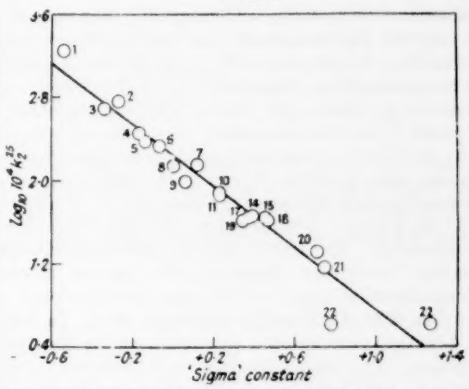


FIG. 1. *Relation between heat of activation and the logarithm of the rate constant (at 25°) for substituted azobenzenes. The line is drawn through the point for azobenzene at a slope of −2·303 RT. The key to the numbers is given in the Table.*

FIG. 2. *Relation between the logarithm of the rate constant (at 25°) and the Hammett "sigma" constant for the particular substituent. The key to the numbers is given in the Table.*

constants for the disubstituted compounds fall accurately on the curve (Fig. 2) when plotted against the sum of the relevant sigma constants.

2 : 2′-Dimethylazobenzene reacted more slowly than azobenzene and much more slowly than 4 : 4′-dimethylazobenzene. Steric hindrance is evidently a factor here, for the $T(\Delta S^{\ddagger} - \Delta S_0^{\ddagger})$ value is somewhat greater than that for the *meta*- and *para*-substituted derivatives. Moreover, the absorption spectra of 2 : 2′-dimethylazobenzene and of its azoxy-derivative (Part IV, *J.*, 1953, 2156) indicate that the latter compound is sterically hindered.

Most of the substituted azo-compounds used in this investigation were prepared by standard methods, but some improvements in experimental procedure have been effected. 3- and 4-Fluoroazobenzene were prepared by condensing nitrosobenzene with the appropriate fluoroaniline. 4-Thiocyanatoazobenzene was prepared from *p*-thiocyanatoaniline and nitrosobenzene, but it was unsuitable for examination as perbenzoic acid oxidised the substituent. 4-Thiocyanatoazobenzene was also found to be converted by passage through a column of alumina into a sparingly soluble product which is probably the disulphide, $NPh{:}N{\cdot}C_6H_4{\cdot}S{\cdot}S{\cdot}C_6H_4{\cdot}N{:}NPh$. A similar conversion of a thiocyanato-derivative into a disulphide has been reported by Wood and Fieser (*J. Amer. Chem. Soc.*, 1941, **63**, 2323).

Application to Problem of Carcinogenesis.—The observed linear relationship between

the logarithm of the rate constant and the Hammett sigma constant is of some importance. It implies that the electron density around the azo-nitrogen atoms in substituted azobenzenes is directly related to the sigma constants of the substituents, and this is of value in determining the relative electron densities at this region in the carcinogenic compounds. For example, the relative electron densities in a series of substituted 4-dimethylaminoazobenzenes can be evaluated in terms of the sigma constants for the " additional " substituents. Unfortunately, relatively few 3'- and 4'-substituted 4-dimethylaminoazobenzenes have so far been tested for carcinogenic activity, and no firm conclusions can be reached. The available data (Badger and Lewis, *loc. cit.*) are, however, not inconsistent with the view that carcinogenic activity is related to an optimum electron density around the azo-nitrogen atoms.

Experimental

Mono-substituted Azobenzenes.—Most of the mono-substituted azobenzenes were prepared by condensing nitrosobenzene with the appropriate substituted aniline, the temperature being kept below 30° (cf. Hickinbottom, " Reactions of Organic Compounds," p. 326). Except 3-methylazobenzene, all the products separated from the reaction mixture as solids. The crude material was purified by chromatography on alumina from light petroleum, elution being effected with solutions of 10%, 20%, and then 30% benzene in light petroleum. After evaporation of the solvent the azo-compound was recrystallised from alcohol. 3-Methylazobenzene was first obtained as an oil, but after purification in the above manner, it had m. p. 20° (lit. 18°). 3-*Fluoroazobenzene*, prepared from *m*-fluoroaniline, was obtained as orange plates, m. p. 44° (Found: C, 72·1; H, 4·6. $C_{12}H_9N_2F$ requires C, 72·0; H, 4·5%). 4-*Fluoroazobenzene*, prepared from *p*-fluoroaniline, was obtained as orange-yellow needles, m. p. 83° (Found: C, 72·3; H, 4·7%). The crude product obtained by condensing *p*-thiocyanatoaniline with nitrosobenzene was purified by recrystallisation from alcohol. The 4-*thiocyanatoazobenzene* thus obtained formed pale orange plates, m. p. 72° (Found: C, 65·2; H, 3·8. $C_{13}H_9N_3S$ requires C, 65·3; H, 3·8%). Attempted purification of this compound by chromatography on alumina was unsuccessful. A sparingly soluble substance separated out on the column and this could only be removed from the alumina with boiling chloroform. Evaporation of the solvent and recrystallisation from alcohol gave the *disulphide* as orange plates, m. p. 166° (Found: C, 67·6; H, 4·2. $C_{24}H_{18}N_4S_2$ requires C, 67·6; H, 4·2%).

4-Methoxyazobenzene was obtained by methylation of 4-hydroxyazobenzene with methyl sulphate. 4-Chloroazobenzene was obtained from 4-aminoazobenzene by the Sandmeyer reaction; and 3-methoxyazobenzene was obtained from nitrobenzene, *m*-anisidine, and sodium hydroxide at 170—180° (Martynoff, *Bull. Soc. chim.*, 1951, 214), the product being purified by chromatography.

4-Nitro- and 4 : 4'-dinitro-azobenzene were prepared by direct nitration of azobenzene (Werner and Stiasny, *Ber.*, 1889, **22**, 3268). The crude product was extracted with light petroleum (Soxhlet) for 24 hr. Evaporation of the solvent and repeated recrystallisation from glacial acetic acid gave 4-nitroazobenzene, m. p. 145°. The fraction insoluble in light petroleum was repeatedly recrystallised from glacial acetic acid and gave 4 : 4'-dinitroazobenzene, m. p. 223°.

Di-substituted Azobenzenes.—All the di-substituted azobenzenes were prepared from the appropriate nitrobenzene as follows: A mixture of the substituted nitrobenzene (1 mole), and sodium hydroxide (150 g.) in water (150 c.c.) and alcohol (600 c.c.) was treated with zinc dust (350 g.) in small portions at a rate sufficient to maintain vigorous boiling. After all the zinc dust had been added, the reaction mixture was heated for another 2 hr. on the water-bath. The mixture was then filtered, and the zinc residues washed with boiling alcohol (500 c.c.). Air was then drawn through the solution for 6 hr. (to oxidise any hydrazo-compound), and the crude azo-compound collected. Purification was effected by recrystallisation, but in each case the purity of the product was checked by a trial chromatographic analysis. No bands due to impurites were observed.

Reaction.—Rates of reaction with perbenzoic acid were determined by the method outlined in Part I for *trans*-azobenzene.

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442. *Aromatic Azo-compounds. Part III.* Oxidation of Azonaphthalenes and Phenylazonaphthalenes.*

By G. M. Badger and G. E. Lewis.

The rates of oxidation of the two phenylazonaphthalenes and of the three azonaphthalenes with perbenzoic acid have been determined at four temperatures. The energies of activation have been calculated, and the results interpreted in terms of the extent of conjugation of the azo-group with the ring system, and of steric hindrance.

It is concluded that the carcinogenic substance, 2 : 2′-azonaphthalene, is *not* closely related to the carcinogenic aminoazo-compounds.

Although most of the azo-compounds which produce liver cancers in experimental animals are amino-derivatives, a few carcinogens are known which do not possess an amino-group. 2 : 2′-Azonaphthalene produces liver tumours in mice, and 1 : 1′-azonaphthalene also has slight activity; but 1 : 2′-azonaphthalene is inactive (Cook, Hewett, Kennaway, and Kennaway, *Amer. J. Cancer*, 1940, **40**, 62). It seemed of interest to examine the azonaphthalenes and phenylazonaphthalenes in the light of Pullman's hypothesis (*Compt. rend.*, 1946, **222**, 1501; 1947, **224**, 1773; Pullman and Pullman, *Rev. Sci.*, 1946, **84**, 145), and the rates of oxidation of these unsubstituted azo-compounds with perbenzoic acid have accordingly been determined.

The reactions were carried out as described in Part I (*J.*, 1953, 2143), and a preliminary note on the rate constants at 25° for the azonaphthalenes has been published (Badger and Lewis, *Nature*, 1951, **167**, 403). The rates of reaction have now been determined at four temperatures, and the results are summarised in Table 1, the rate constants for *trans*-azobenzene being included for reference.

Table 1. *Rate constants and activation energies for reaction between azo-compounds and perbenzoic acid.**

Azo-naphthalene	10^3k_2 (mole^{-1} min.$^{-1}$ l.) 15°	20°	25°	30°	$\Delta H^\ddagger$ (kcal.)	X	Y	Z
(Azobenzene)	5·80 ± 0·07	9·02 ± 0·15	13·9 ± 0·3	20·9 ± 0·3	14·8 ± 0·3	0	0	0
2-Phenyl- ...	6·03 ± 0·10	9·40 ± 0·16	14·5 ± 0·3	22·3 ± 0·3	15·1 ± 0·4	+0·3	+0·3	0
2 : 2′-	7·23 ± 0·09	11·5 ± 0·2	17·6 ± 0·4	26·6 ± 0·3	15·1 ± 0·3	+0·3	+0·4	−0·1
1-Phenyl- ...	6·10 ± 0·1	9·46 ± 0·18	14·5 ± 0·3	22·2 ± 0·3	14·9 ± 0·4	+0·1	+0·1	0
1 : 2′-	7·34 ± 0·1	11·6 ± 0·2	17·7 ± 0·3	26·8 ± 0·3	15·0 ± 0·3	+0·2	+0·3	−0·1
1 : 1′-	0·89 ± 0·024	1·52 ± 0·07	2·46 ± 0·11	4·05 ± 0·06	17·5 ± 0·5	+2·7	+1·7	+1·0

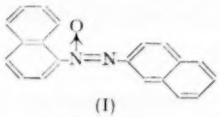
* $\Delta H_0^\ddagger$, $\Delta S_0^\ddagger$, and $\Delta F_0^\ddagger$ refer to the heat of activation, entropy of activation, and free energy of activation, respectively, for *trans*-azobenzene. $X = \Delta H^\ddagger - \Delta H_0^\ddagger$; $Y = T(\Delta S^\ddagger - \Delta S_0^\ddagger)$; $Z = \Delta F^\ddagger - \Delta F_0^\ddagger$; all in kcal. The quantities $T(\Delta S^\ddagger - \Delta S_0^\ddagger)$ and $\Delta F^\ddagger - \Delta F_0^\ddagger$ were calculated from the data at 25°.

The azoxy-compound was isolated from the reaction mixture in each case. 2 : 2′-Azonaphthalene was oxidised more rapidly than azobenzene, giving 2 : 2′-azoxynaphthalene. 1 : 1′-Azonaphthalene was oxidised rather more slowly, and gave the azoxy-compound. In the following paper (Part IV), it is shown that the *peri*-hydrogen atoms offer steric interference with the oxygen atom in 1 : 1′-azoxynaphthalene, and that this molecule cannot be coplanar. It is reasonable to conclude, therefore, that steric hindrance must be a factor in all oxidations which take place at an azo-nitrogen atom which is adjacent to the 1-position in naphthalene.

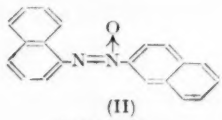
Only one azoxy-compound was obtained by oxidation of 1 : 2′-azonaphthalene and this is regarded as having the "β"-structure (II). This is supported by spectrographic evidence (Part IV), and also by the fact that 1 : 2′-azonaphthalene was oxidised at almost

* Part II, preceding paper.

the same rate as 2 : 2′-azonaphthalene. The azo-nitrogen atom adjacent to the 1-position is sterically hindered, and the isomeric azoxy-compound (I) seems not to be formed at all.

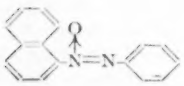


(I)
" α "-Isomer

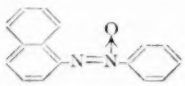


(II)
" β "-Isomer

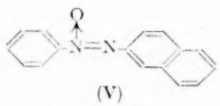
Oxidation of 1-phenylazonaphthalene likewise gave only one azoxy-compound, and spectrographic evidence (Part IV) indicates that this must be the " β "-isomer (IV). This structure is supported by the fact that the same compound was also obtained as a by-product in the preparation of 1-phenylazonaphthalene by condensation of nitrobenzene and 1-naphthylamine in the presence of sodium hydroxide at 170° (Martynoff, *Bull. Soc. chim.*, 1951, 214). It is true that the mechanism of this reaction requires elucidation, but it is significant that the isomeric azoxy-compound (III) could not be isolated from the reaction mixture.



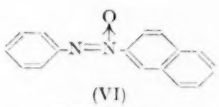
(III)
" α "-Isomer



(IV)
" β "-Isomer



(V)
" α "-Isomer



(VI)
" β "-Isomer

The oxidation of 2-phenylazonaphthalene gave an azoxy-compound, which, after recrystallisation, had m. p. 98°, and was at first thought to be homogeneous. It was subsequently found, however, that this product is a eutectic mixture of the two azoxy-compounds (V and VI) of m. p. 125° and 117°. The crude oxidation product seems to contain about 41% of the isomer of m. p. 125° and 59% of that of m. p. 117°. This ratio is almost the same as the ratio of the reaction rates of azobenzene and 2 : 2′-azonaphthalene (Table 1), so the isomers are regarded as having respectively the " α "- and the " β "-structure, (V) and (VI). This conclusion is supported by the fact that the isomer of m. p. 125° was also obtained as a by-product in the condensation of nitrobenzene with 2-naphthylamine in the presence of sodium hydroxide at 180° (cf. Ramart-Lucas, Guilmart, and Martynoff, *Bull. Soc. chim.*, 1947, 424). None of the isomeric azoxy-compound, m. p. 117°, was obtained in this reaction; had any been formed, a mixture of this isomer with the azoxy-derivative, m. p. 125°, would have been isolated, for the eutectic cannot be separated into its components by chromatography on alumina.

Discussion.—The oxidation of azo-compounds with perbenzoic acid exhibits second-order kinetics, and can be represented by the equation :

$$\mathrm{Ar{-}\overset{\cdot\cdot}{N}{=}\overset{\cdot\cdot}{N}{-}Ar' + Ph{\cdot}CO_3H = Ar{-}\overset{\cdot\cdot}{N}(\rightarrow O){=}\overset{\cdot\cdot}{N}{-}Ar' + Ph{\cdot}CO_2H}$$

Substituents may be expected to have a profound influence on the electron density around the nitrogen atoms, and it has been shown (Part II) that they have a considerable influence on the rate of reaction and on the energy of activation.

The azo-group is, of course, conjugated with the ring system, and with unsubstituted compounds the extent of conjugation must be a most important variable, depending on the ring system and the position of the azo-group. The greater the conjugation, the smaller must be the bond order of the N=N bond and the smaller the " availability " of the nitrogen " lone pairs."

According to Coulson and Longuet-Higgins (*Proc. Roy. Soc.*, 1948, *A*, **195**, 188) the conjugating power of a position is β times the self-polarisability of that position, as calculated by the method of molecular orbitals. It has also been shown that the free-valence number (whether calculated by the method of molecular orbitals, or by the valence-bond method) can also be used as an index of conjugating ability (Pullman, *Compt. rend.*, **1946**, **222**, 1396; Daudel, *ibid.*, 1950, **230**, 99).

The calculated values for the 1- and the 2-position in naphthalene and for a phenyl ring are given in Table 2. All three methods indicate that the 1-position in naphthalene has a greater conjugating ability than the 2-position, and that this in turn is very slightly greater than the conjugating ability of a phenyl ring. The available experimental evidence (Badger, Pearce, and Pettit, *J.*, **1952**, 1112) also indicates that the 1-position of naphthalene has a much greater conjugating ability than the 2-position.

TABLE 2. *Conjugating abilities of the two positions in naphthalene and in benzene.*

	Index of conjugating ability		
Position	Self polarisability * (M.O. method)	Free valence number † (M.O. method)	Free valence number ‡ (V.B. method)
1-Naphthyl	**0·443**	0·134	0·122
2-Naphthyl	0·405	0·086	0·098
Phenyl	0·398	0·081	0·073

* These values should be multiplied by $1/\beta$ (Coulson and Longuet-Higgins, *loc. cit.*).
† Burkitt, Coulson, and Longuet-Higgins, *Trans. Faraday Soc.*, 1951, **47**, 553.
‡ Pullman, *Ann. Chim.*, 1947, **2**, 5.

This is reflected in the bond orders of the ethylenic bond in stilbene and in the dinaphthylethylenes (Coulson, *J.*, **1950**, 2252). The ethylenic bond in stilbene has a bond order of 1·820, that in 2 : 2′-dinaphthylethylene of 1·814, and that in 1 : 1′-dinaphthylethylene of 1·792 : *i.e.*, the greater the conjugation, the smaller the bond order.

It is well known that there is a smooth-curve relationship between the bond orders of carbon–carbon bonds and their length, but it does not seem to be so well known that a similar relationship holds for nitrogen–nitrogen bonds, the two curves being very nearly parallel. It is resonable to suppose, therefore, that the bond orders of the N=N bonds in azobenzene and in the azonaphthalenes will parallel those of the C=C bonds in stilbene and the dinaphthylethylenes. Buu-Hoï *et al.* (*Bull. Soc. chim.*, **1951**, **18**, 132c) have calculated that the N=N bond in azobenzene has a bond order of 1·746; 2 : 2′-azonaphthalene must therefore have a bond order slightly less than this, and 1 : 1′-azonaphthalene must have a still smaller bond order. Moreover, as the conjugating ability is the controlling factor in each case, the "availability" of the nitrogen "lone pairs" must clearly vary in the same sequence.

Of the six compounds included in Table 1, two undergo oxidation at an azo-nitrogen which is adjacent to a phenyl ring, two are attacked at a nitrogen adjacent to a 2-position in naphthalene, and one (2-phenylazonaphthalene) gives a mixture of two azoxy-compounds. It should therefore be possible to avaluate the relative conjugating abilities of a phenyl ring and of the 2-position in naphthalene.

As Hammett has pointed out ("Physical Organic Chemistry," McGraw-Hill, **1940**, pp. 118 *et seq.*). when the entropy of activation ($\Delta S^{\ddagger}$) is constant for a series of related compounds, the equation, $\Delta H^{\ddagger} = \Delta F^{\ddagger} - T\Delta S^{\ddagger}$, reduces to $\Delta H^{\ddagger} = \Delta F^{\ddagger}$. In these circumstances, differences in the heats of activation and in the free energies of activation have the same significance, and both are equal to the potential-energy change for the reaction. The experimental determination of the free energy of activation, however, is much more accurate than that of the heat of activation. Furthermore, differences in potential energy can be associated almost entirely with changes in electron density at the reacting centre.

For the five compounds which are oxidised at a nitrogen atom adjacent to either a phenyl ring or a 2-position in naphthalene, the entropies of activation are found to be constant [*i.e.*, $T(\Delta S^{\ddagger} - \Delta S_0^{\ddagger}) \sim 0$], within experimental error. The heats of activation and the free energies of activation are found to be almost identical. Therefore, in spite of the fact that there are some differences in the rates of reaction, it can only be concluded that the electron densities around the nitrogen atoms in these compounds are very nearly equal. This conclusion is in substantial agreement with the theoretical work (Table 2) which indicates that the 2-position in naphthalene has a conjugating ability which is only very slightly greater than that of a phenyl ring.

In the case of 1 : 1′-azonaphthalene, steric hindrance is clearly a factor, in addition to

the increased conjugating ability of the 1-position. It reacts very much more slowly than its isomers, and has a much greater heat of activation. The steric factor is also confirmed by the significant increase in the entropy of activation compared with either azobenzene or 2 : 2′-azonaphthalene.

Application to Problem of Carcinogenesis.—The results clearly indicate that the liver carcinogen, 2 : 2′-azonaphthalene, has an electron density around the nitrogen atoms which is almost the same as that in the non-carcinogenic substances, azobenzene and 1 : 2′-azonaphthalene. Moreover, this electron density must be very much below the value for the carcinogenic aminoazo-compounds such as *o*-aminoazotoluene and 4-dimethylaminoazobenzene (see Part II).

If it is assumed that Pullman's hypothesis is valid for the aminoazo-compounds, then it can only be concluded that 2 : 2′-azonaphthalene must act by a different mechanism. As a matter of fact this seems not unlikely. 2 : 2′-Azonaphthalene produces liver tumours in mice, but not in rats (Cook, Hewett, Kennaway, and Kennaway, *loc. cit.*; Badger, Lewis, and Reid, unpublished), although the aminoazo-compounds are quite active in the latter species.

Furthermore, it has been suggested (Cook, Hewett, Kennaway, and Kennaway, *loc. cit.*) that 2 : 2′-azonaphthalene is not active *per se*, but that it is converted into a carcinogenic substance in the liver of the mouse. It was suggested that it may be reduced *in vivo* to the hydrazo-derivative and that it may subsequently undergo the benzidine rearrangement and loss of ammonia to give 3 : 4-5 : 6-dibenzocarbazole; this substance is certainly a potent carcinogen, and although there is no direct evidence that this conversion does take place, all the available data are consistent with this view. The slight carcinogenic activity of 1 : 1′-azonaphthalene can be explained by its analogous conversion into the slightly carcinogenic 1 : 2-7 : 8-dibenzocarbazole. The aminoazo-compounds, however, may not owe their activity to a metabolic transformation of this type, but may act by a different mechanism; and with these compounds the amino-group may well be an essential feature.

Experimental

1 : 1′-*Azonaphthalene.*—This was prepared by the action of sodium sulphite and sodium acetate on diazotised 1-naphthylamine according to Cohen and Oesper (*Ind. Eng. Chem., Anal.*, **1936, 8,** 306). It was purified by chromatography on alumina from light petroleum. Development was carried out with light petroleum containing 10%, 20%, and then 30% of benzene. The 1 : 1′-azonaphthalene was less strongly adsorbed and was sharply separated from impurities which were retained near the top of the column. After evaporation of solvent and recrystallisation from ethanol, it had m. p. 190°.

2 : 2′-*Azonaphthalene.*—2-Naphthylamine was diazotised and treated with sodium sulphite and sodium acetate exactly as above. The crude product was recrystallised from 50 : 50 light petroleum–benzene (charcoal) and had m. p. 208°, unchanged after chromatography.

1 : 2′-*Azonaphthalene.*—4-Amino-1 : 2′-azonaphthalene was diazotised in alcohol, and the mixture boiled (Nietzki and Göttig, *Ber.*, **1887, 20,** 612). The tarry product was precipitated by water and extracted with light petroleum. After several washes with water, the solution was dried (Na_2SO_4) and passed through a column of alumina; development and elution as before gave a sharp separation of the product. After evaporation of solvent and recrystallisation from alcohol, the 1 : 2′-azonaphthalene had m. p. 145° (yield 45%).

1-*Phenylazonaphthalene.*—(i) 4-Phenylazo-1-naphthylamine was diazotised in alcohol, and the mixture boiled (Nietzki and Zehntner, *Ber.*, **1893, 26,** 143). The crude product was purified as for 1 : 2′-azonaphthalene. After a final recrystallisation from ethanol, 1-phenylazonaphthalene had m. p. 70° (yield 50%).

(ii) For the preparation of a large quantity of material, Martynoff's method (*loc. cit.*) was more satisfactory. After purification by chromatography and recrystallisation, 1-phenylazonaphthalene, m. p. 70°, was obtained. A small band following immediately after 1-phenylazonaphthalene on the chromatogram was also eluted. Evaporation of the solvent and recrystallisation from alcohol gave " β "-1-phenylazoxynaphthalene m. p. 84°, identical with the product (see below) obtained by oxidation of 1-phenylazonaphthalene with perbenzoic acid.

2-*Phenylazonaphthalene.*—This was prepared in quantity by condensing nitrobenzene with 2-naphthylamine in the presence of sodium hydroxide at 180° (Ramart-Lucas, Guilmart, and

Martynoff, *loc. cit.*). After purification by chromatography and recrystallisation from alcohol, it had m. p. 84°. A small band immediately following the 2-phenylazonaphthalene on the chromatogram was also eluted. Evaporation of the solvent and recrystallisation from alcohol gave " α "-2-phenylazoxynaphthalene, m. p. 125°, alone or admixed with a specimen isolated after oxidation of 2-phenylazonaphthalene with perbenzoic acid (see below).

After elution of the 2-phenylazonaphthalene and the small amount (100 mg. in 50-g. preparation) of 2-phenylazoxynaphthalene, a pale yellow band followed. It was eluted with 65% benzene in light petroleum. Evaporation of the solvent and recrystallisation from alcohol gave 1 : 2-benzophenazine as very pale yellow needles, m. p. 142° (Found : C, 83·5; H, 4·5; N, 12·5. Calc. for $C_{16}H_{10}N_2$: C, 83·5; H, 4·35; N, 12·2%). The m. p. was not depressed by admixture of the compound with an authentic specimen, and the absorption spectrum was identical with the published curve (Badger, Pearce, and Pettit, *J.*, 1951, 3199).

Isolation of Azoxy-compounds.—When the oxidation was virtually complete in each case, the reaction mixture was washed with dilute sodium carbonate and then with water, and the solvent evaporated. The crude product was then separated from traces of impurities by chromatography on alumina from light petroleum (benzene–light petroleum being used for elution). The product was finally crystallised from alcohol. (i) 1 : 1′-Azonaphthalene gave 1 : 1′-azoxynaphthalene, m. p. 127° (lit. 127°). (ii) 2 : 2′-Azonaphthalene gave 2 : 2′-azoxynaphthalene, m. p. 166° (lit. 164°). (iii) 1 : 2′-Azonaphthalene gave " β "-1 : 2′-*azoxynaphthalene* (II) as bright yellow needles, m. p. 137° (Found : C, 80·8; H, 4·6. $C_{20}H_{14}ON_2$ requires C, 80·5; H, 4·7%). (iv) 1-Phenylazonaphthalene gave " β "-1-*phenylazoxynaphthalene* (IV) as bright yellow needles, m. p. 84° (Found : C, 77·65; H, 4·9. $C_{16}H_{12}ON_2$ requires C, 77·4; H, 4·9%). The m. p. was not depressed by admixture with a specimen prepared from nitrobenzene and 1-naphthylamine with sodium hydroxide (see above).

(v) Oxidation of 2-phenylazonaphthalene gave an azoxy-compound which, after chromatography, had m. p. 98·1—99·3°. Recrystallisation from alcohol gave a product melting constantly at 98°, unchanged after careful chromatography. Very slow recrystallisation from a large volume of light petroleum (b. p. 90—120°), however, deposited a small amount of material which on recrystallisation from alcohol gave pure " α "-2-*phenylazoxynaphthalene* (V) as yellow prisms, m. p. 125° (Found : C, 77·1; H, 5·1; N, 11·5; O, 6·4. $C_{16}H_{12}ON_2$ requires C, 77·4; H, 4·9; N, 11·3; O, 6·45%). The m. p. was not depressed by admixture with a specimen prepared from nitrobenzene and 2-naphthylamine with sodium hydroxide (see above). The structure was confirmed by reduction to 2-phenylazonaphthalene with lithium aluminium hydride.

The other azoxy-compound was isolated following an attempt to brominate the crude product (m. p. 98·1—99·3°) in carbon tetrachloride. After 2 hr. at 0° and then 4 hr. on a water-bath, the excess of bromine was removed by shaking with sodium thiosulphate solution. After removal of the solvent, the residue was treated with a little light petroleum (b. p. 40—60°). The less soluble fraction was chromatographed on alumina from light petroleum in the usual way, and crystallisation of the product from alcohol gave pure " β "-2-*phenylazoxynaphthalene* as pale yellow needles, m. p. 117° (Found : C, 77·65, 77·4; H, 5·0, 4·9%). The product did not contain bromine and it was readily reduced to 2-phenylazonaphthalene with lithium aluminium hydride.

The eutectic for the binary system was found by the " thaw-melt " method to have the composition of 42·5% of the isomer, m. p. 125°, and 57·5% of the isomer, m. p. 117°. The m. p. of the perbenzoic acid oxidation product (98·1—99·3°) was depressed by the addition of a very small amount of isomer, m. p. 125°, and the product therefore had approximately the composition given on p. 2152.

Rate Determinations.—Rates of reaction were determined exactly as for *trans*-azobenzene (Part I), three determinations being carried out at each temperature.

We thank Dr. J. C. D. Brand, Dr. H. H. G. Jellinek, and Dr. R. I. Reed for helpful discussions. We also thank the C.S.I.R.O. for a scholarship awarded to one of us (G. E. L.). Microanalyses were carried out at the C.S.I.R.O. Microanalytical Laboratory, Melbourne.

UNIVERSITY OF ADELAIDE. [*Received, January 14th,* 1953]

443. *Aromatic Azo-compounds. Part IV.* Absorption Spectra of Azo- and Azoxy-compounds.*

By G. M. Badger and R. G. Buttery.

The absorption spectra of the azonaphthalenes and phenylazonaphthalenes have been examined, and it has been found that the position of the *K*-absorption band can be correlated with the degree of conjugation.

Several azoxy-compounds have also been examined. In most cases, there is a bathochromic shift in passing from the azo- to the azoxy-compound; but with 1 : 1′-azoxynaphthalene and *oo*′-azoxytoluene there is a pronounced hypsochromic shift. This is probably due to steric hindrance to coplanarity.

The spectra of aromatic azo-compounds usually show several regions of absorption. There is generally a band or bands in the region **2100—2900** Å, probably due to absorption by the aromatic rings, and azobenzene and some substituted azobenzenes also show a weak absorption band at about **4400—4700** Å, evidently due to the N:N linkage itself. However, the intense band at about **3200—3700** Å has been ascribed to conjugation between the N:N group and the aromatic nuclei, and it can be shown that substituents (*e.g.*, in the *p*-positions) which increase this conjugation shift this absorption band to longer wavelengths (Burawoy, *J.*, **1937**, 1865; Cook, Jones, and Polya, *J.*, 1939, 1315). It was therefore decided to determine the absorption spectra of the azonaphthalenes, the phenylazonaphthalenes, and their azoxy-derivatives.

All the compounds examined have been found to have three main regions of absorption, and these have been called regions I, Ia, and II. Region I contains a single peak of high intensity at about **2200** Å, and this evidently corresponds to a similar peak at **2210** Å in the spectrum of naphthalene (cf. Mayneord and Roe, *Proc. Roy. Soc.*, 1935, *A*, **152**, 299). Region Ia contains 1—3 peaks at about **2650**, **2750**, and **2900** Å, and these apparently correspond to the three peaks in the spectrum of naphthalene at **2660**, **2750**, and **2850** Å. Region II is usually a broad band of high intensity around **3200—3800** Å. This is the band which Burawoy (*loc. cit.*) ascribed to conjugation between the azo-linkage and the

Positions of the maxima (in Å*) and corresponding* log ε *values in the absorption spectra of azo- and azoxy-compounds (solvent, ethanol).*

Compound	Region I	Region Ia			Region II, *K*-band
Azobenzene	—	2290 (4·11)	—	—	3180 (4·32)
2-Phenylazonaphthalene	2190 (4·48)	2650 (4·13)	2770 (4·13)	2870 (4·13)	3280 (4·28)
2 : 2′-Azonaphthalene	2140 (4·57)	2620 (4·39)	2780 (4·28)	2900 (4·18)	3350 (4·37)
1-Phenylazonaphthalene	2190 (4·58)	2660 (4·03)	2730 (4·03)	2900 (3·94)	3720 (4·10)
1 : 2′-Azonaphthalene	2160 (4·76)	2640 (4·35)	—	3100 (4·02)	3810 (4·24)
1 : 1′-Azonaphthalene	2140 (4·87)	2660 (4·26)	—	—	4000 (4·21)
Azoxybenzene	2310 (3·93)	2610 (3·87)	—	—	3230 (4·16)
"α"-2-Phenylazoxynaphthalene (m. p. 125°)	2160 (4·51)	—	2760 (4·28)	2850 (4·23)	3400 (4·30)
"β"-2-Phenylazoxynaphthalene (m. p. 117°)	2140 (4·59)	2410 (4·15)	2590 (4·24)	2910 (4·08)	3310 (4·30)
2 : 2′-Azoxynaphthalene	2160 (4·71)	2630 (4·41)	2770 (4·37)	(2890) (4·24)	3460 (4·41)
"β"-1-Phenylazoxynaphthalene	2200 (4·54)	2690 (4·12)	—	—	3780 (4·06)
"β"-1 : 2′-Azoxynaphthalene	2160 (4·76)	(2540) (4·25)	2620 (4·29)	2910 (4·04)	3860 (4·17)
1 : 1′-Azoxynaphthalene	2180 (4·93)	2620 (4·11)	—	(2880) (3·91)	3640 (4·06)
oo′-Azotoluene	—	2350 (3·98)	—	—	3320 (4·24)
oo′-Azoxytoluene	—	2350 (3·96)	—	—	3110 (3·94)

aromatic rings, and which he called the "*K*-band." Burawoy's *R*-band is difficult to identify in the spectra of the azonaphthalenes and phenylazonaphthalenes as it is usually only a point of inflexion. This band seems to be absent in the azoxy-compounds.

* Part III, preceding paper.

The positions and intensities of the absorption maxima for these compounds are recorded in the table, and the results clearly show that the *K*-band is shifted to longer wave-lengths with increasing conjugation. The *K*-band for azobenzene is at **3180**, that for **2 : 2'**- at **3350**, and that for **1 : 1'**-azonaphthalene at **4000 Å**. It seems that this generalisation holds quite accurately. The conjugating power of a position in an aromatic ring can be defined as β times the self-polarisability of that position (Coulson and Longuet-Higgins, *Proc. Roy. Soc.*, **1948**, *A*, **195**, 188), and for the azo-compounds the most satisfactory index of the conjugation is probably obtained by summing the self-polarisabilities

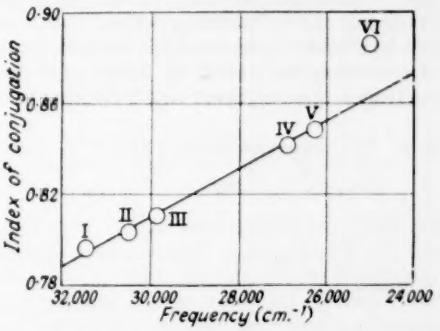


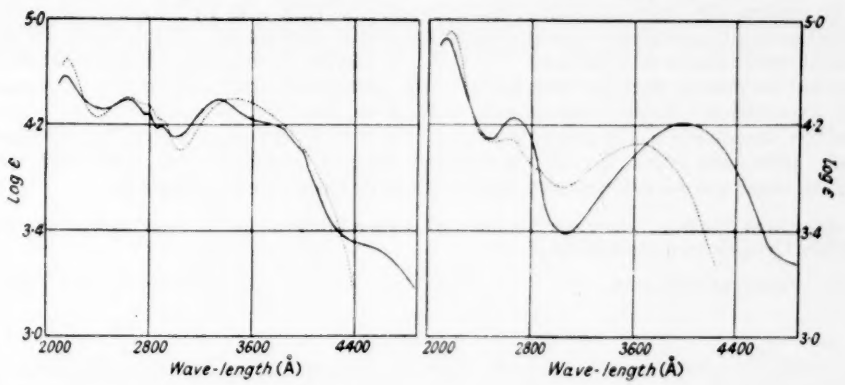
FIG. 1. *The relation between the frequency of the K-absorption band and the sum of the self-polarisabilities of the positions to which the* N:N *group is attached.*

(I) *Azobenzene.*
(II) *2-Phenylazonaphthalene.*
(III) *2 : 2'-Azonaphthalene.*
(IV) *1-Phenylazonaphthalene.*
(V) *1 : 2'-Azonaphthalene.*
(VI) *1 : 1'-Azonaphthalene.*

of the two positions to which the azo-group is attached. The self-polarisability of any position in a phenyl ring is **0·398**, so the index of conjugation for azobenzene is **0·796**; the self-polarisability of the 2-position in naphthalene is **0·405**, so the index of conjugation for 2-phenylazonaphthalene is **0·803**; the self-polarisability of the 1-position in naphthalene is **0·443**, so the index of conjugation for 1-phenylazonaphthalene is **0·841**; and so on. On using these data, there is seen to be a remarkable degree of correlation between the index of conjugation and the frequency of the *K*-absorption band (Fig. 1).

FIG. 2. *Absorption spectra of* **2 : 2'***-azonaphthalene* (———), *and of* **2 : 2'***-azoxynaphthalene* (. . . . .), *both in ethanol.*

FIG. 3. *Absorption spectra of* **1 : 1'***-azonaphthalene* (———), *and of* **1 : 1'***-azoxynaphthalene* (. . . . .), *both in ethanol.*



The degree of conjugation is also indicated by other details in the spectra. For example, the spectrum of **2 : 2'**-azonaphthalene in the Ia region is very similar to that of naphthalene, three peaks being resolved. On the other hand, the increased conjugation in the case of **1 : 1'**-azonaphthalene evidently disturbs the electronic configuration, and the Ia region for this compound shows only one absorption maximum. The spectrum of **1 : 2'**-azonaphthalene is intermediate, and two peaks have been resolved in this region.

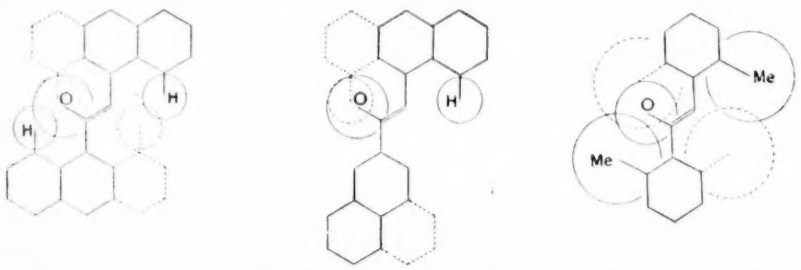
The spectra of the azoxy-compounds were found to resemble those of the corresponding

azo-compounds very closely. Three main regions of absorption (I, Ia, and II) were again distinguished (see table); but no *R*-band or point of inflexion corresponding to the *R*-band (Burawoy, *loc. cit.*) could be detected.

In region II (*K*-band), with one exception, there is a *bathochromic* shift of about **70** Å in passing from an azo- to the corresponding azoxy-compound. In 1 : 1′-azonaphthalene, however, the introduction of the oxygen atom produced a *hypsochromic* shift of about **360** Å (Figs. 2 and 3).

The construction of scale models and of scale diagrams (Fig. 4) indicates that if the oxygen atom is attached to an azo-nitrogen atom adjacent to the 1-position in naphthalene, the molecule cannot assume a coplanar configuration. In these circumstances, conjugation would be inhibited and absorption would occur at shorter wave-lengths (cf. Beale and Roe, *J. Amer. Chem. Soc.*, 1952, **74**, 2302). On the other hand, if the oxygen is attached to an azo-nitrogen atom adjacent to a 2-position in naphthalene or to a phenyl ring, the molecule

Fig. 4. 1 : 1′-*Azoxynaphthalene.* Fig. 5. 1 : 2′-*Azoxynaphthalene.* Fig. 6. oo′-*Azoxytoluene.*



can assume a coplanar configuration (Fig. 5), and absorption occurs at a slightly longer wave-length than with the azo-compound itself. This indicates that the azoxy-compounds which are obtained by oxidation of 1-phenylazonaphthalene and of 1 : 2′-azonaphthalene cannot have the oxygen on the nitrogen atom adjacent to the 1-position of the naphthalene ring, and that these derivatives must have the alternative structures assigned to them in Part III (preceding paper).

To confirm this interpretation of the hypsochromic shift with 1 : 1′-azoxynaphthalene, it was decided to examine *oo*′-azoxytoluene, for a scale diagram (Fig. 6) indicated that this molecule must also be non-coplanar. In this case a hypsochromic shift of about **200** Å was observed on passing from *oo*′-azotoluene to the azoxy-derivative, in complete agreement with expectation. Small bathochromic shifts have, however, been observed on passing from *mm*′-azotoluene to the azoxy-derivative, and from *pp*′-azotoluene to *pp*′-azoxytoluene (Cook, Jones, and Polya, *loc. cit.*; Müller and Hory, *Z. physikal. Chem.*, 1932, **162**, 281). In these *meta*- and *para*-derivatives, there is no steric hindrance to coplanarity.

Absorption Spectra.—The absorption spectra were all determined, in absolute ethanol, with a Hilger Uvispek Spectrophotometer.

University of Adelaide. [*Received, January* 14*th*, 1953.]

444. *Triterpenoids. The Crystal Structure of Lanostenyl Iodoacetate.*

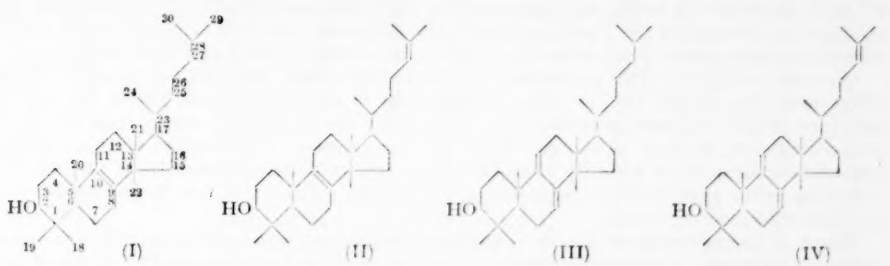
By J. Fridrichsons and A. McL. Mathieson.

The crystal structure of lanostenyl iodoacetate has been determined by *X*-ray analysis. Parameters of all atoms (except hydrogen) have been fixed, providing without ambiguity the structural formula and a detailed stereochemical description of the molecule. Lanostenol has a tetradecahydro-*cyclo*pentenophenanthrene ring system with an inert double bond at $C_{(9)}$–$C_{(10)}$ (triterpenoid notation), the rings A and B and C and D being *trans*-fused. The $C_{(3)}$-hydroxyl group and the $C_{(5)}$- and $C_{(13)}$-methyl groups are β-oriented whereas that at $C_{(14)}$ is α-oriented. The *gem*-dimethyl group is attached to $C_{(4)}$ and the side-chain to $C_{(17)}$.

Distortions arising from the intramolecular packing of methyl groups and from the fusion of the five- to the six-membered rings have been observed. The structure of lanostenol shows remarkable similarity to that of cholesterol.

Wool-wax (for references see the review by Velluz and Lederer, *Bull. Soc. Chim. biol.*, 1945, **27**, 211) contains at least four triterpenoid components: lanostenol (dihydrolanosterol) $C_{30}H_{52}O$ (I), lanostadienol (lanosterol) $C_{30}H_{50}O$ (II), agnostadienol (dihydroagnosterol) or (γ-lanosterol) $C_{30}H_{50}O$ (III), and agnostatrienol (agnosterol) $C_{30}H_{48}O$ (IV). These four compounds are probably based on the same carbon skeleton involving a tetracyclic ring system. Since the solution of the structure of one member would provide a key to those of the other three, lanostenyl iodoacetate was selected as a suitable "heavy-atom" derivative for single-crystal *X*-ray analysis, this technique having been applied with success to steroid molecules of similar complexity: cholesterol (Carlisle and Crowfoot, *Proc. Roy. Soc.*, 1945, *A*, **184**, 64) and calciferol (Crowfoot and Dunitz, *Nature*, 1948, **162**, 608). Structure determination by this method can provide an unequivocal picture of the structure and the stereochemical details of the molecule.

During the present work, Cavalla, McGhie, and Pradhan (*J.*, 1951, 3142), Barton, Fawcett, and Thomas (*J.*, 1951, 3147), Voser, Mijovic, Jeger, and Ruzicka (*Helv. Chim. Acta*, 1951, **34**, 1585), Voser, Guenthard, Jeger, and Ruzicka (*ibid.*, 1952, **35**, 66) and Barnes, Barton, Fawcett, Knight, McGhie, Pradhan, and Thomas (*Chem. and Ind.*, 1951, 1067) have brought forward chemical and spectrophotometric evidence which established an almost complete structural formula for the lanostenol molecule. However, the point of linkage



of the side chain to the ring system has remained in doubt. Barnes, Barton, Fawcett, and Thomas (*J.*, 1952, 2339) favoured $C_{(15)}$ or $C_{(16)}$ on the assumption that the "isoprene rule" holds. In a later publication (*Chem. and Ind.*, 1952, 426), Barnes, Barton, Cole, Fawcett, and Thomas adduced infra-red and chemical evidence which reduced the possibilities to $C_{(15)}$ and $C_{(17)}$, the former again being favoured. Voser, White, Heusser, Jeger, and Ruzicka (*Helv. Chim. Acta*, 1952, **35**, 830) and Mijovic, Voser, Heusser, and Jeger (*ibid.*, p. 964) located the chain at $C_{(17)}$, but have not so far provided experimental evidence for this decision.

No chemical evidence on the stereochemistry of lanostenol has been given previously,

although Barton, Fawcett, and Thomas (*loc. cit.*), on the basis of a ring structure involving four six-membered rings, have offered some comments (*loc. cit.* Fig. V)—omitting any consideration of the influence of the double bond.

Since a brief report of our investigation has been made (*Nature*, 1952, **170**, 221), this paper deals with the detailed structural analysis and discusses the stereochemistry of lanostenol in relation to the other wool-wax triterpenoids, and steroids of similar structure.

Experimental

Crystals of lanostenyl acetate, chloroacetate, and iodoacetate were prepared by Mr. R. Curtis (*J.*, 1950, 1017). Exploratory rotation and moving-films measurements indicated that their unit-cell dimensions differed too greatly for these crystals to be treated as isomorphous. Lanostenyl iodoacetate, $C_{32}H_{53}O_2I$, was therefore selected as the most suitable compound for structure analysis by the "heavy-atom" technique.

Slow cooling of a hot chloroform–methanol solution gave the iodoacetate as thin transparent lath-like crystals, elongated along the *a* axis. The crystals used in recording rotation and Weissenberg photographs were approximately 0·6 × 0·4 × 0·1 mm. The unit cell is orthorhombic with dimensions $a = 7{\cdot}6$, $b = 10{\cdot}9$, and $c = 38{\cdot}6$ Å. Reflections $h00$, $0k0$, and $00l$ are absent in odd orders, indicating the space group $P2_12_12_1$. The density, calculated for four molecules, is 1·24 g./cm.^{3}, the measured value being 1·25 g./cm.^{3}.

An attempt was made to obtain thicker crystals by slow crystallization from various solvents. Crystals from ethyl acetate had nearly perfect square cross-section but on examination were found to be a dimorph with the *a* axis doubled (*i.e.*, eight molecules per unit cell). Only this second form could be obtained on subsequent recrystallizations in this laboratory. Accordingly, the structure analysis had to be carried out on the batch of crystals of the simpler dimorph derived from the earlier crystallizations.

Intensity data for the $0kl$ and $h0l$ reflections were recorded on multiple-film packs, exposed in a Weissenberg goniometer. Two packs, related by timed exposures, were utilised and the intensities were estimated visually against a set of standards, a range of intensities of 1 to 1500 being covered. No corrections for absorption were applied to the intensity data. The structure amplitudes of the two zones were placed on the same scale by correlation of the common $00l$ reflections and were later set on an absolute basis by comparison with the values calculated on the basis of the *f* curves for carbon, oxygen, and iodine, given in the "International Tables" (Bornträger, Berlin, 1936). The temperature factor to be applied to the calculated structure amplitudes, $B = 5{\cdot}75 \times 10^{-16}$ cm.^{2}, was obtained by plotting log $(\Sigma|F_c|/|F_o|)$ against $\sin^2\theta$ over small equal ranges of $\sin^2\theta$.

Fourier summations were carried out by means of three-figure Beevers–Lipson strips with 12° intervals along the *a*- and *b*-axes and 3° intervals along the *c* axis. In the final synthesis for each projection, a better approximation to the correct electron-density distribution was attained by adding into the Fourier synthesis the calculated values of structure amplitudes of reflections whose intensity lay below the limit of observation in the particular experiment.

Structure Analysis.—The parameters of the iodine atoms were derived from Patterson projections, $P(y, z)$ and $P(x, z)$. The contributions of the iodine atoms to the $0kl$ and $h0l$ structure amplitudes were calculated and, since the projections down the *a*- and *b*-axes are centrosymmetric, it could be assumed that the "heavy-atom" contribution would determine correctly the signs of the majority of observed structure amplitudes, except those with small or vanishing iodine contribution; for instance, all $05l$ terms with l odd had to be omitted until the final refinement synthesis.

The first Fourier syntheses for the *a*- and *b*-axis projections were computed with 113 and 63 terms, respectively. The electron-density distribution along the *a*-axis showed ridges of high electron-density, approximately 20 Å long, clearly separated and lying at approximately 30° to the *c*-axis. It was considered that the individual ridges corresponded to an elongated, lath-shaped molecule, with the "plane" of the molecular ring system lying approximately normal to (100) and hence this projection represented an edge-on view of the molecule. There was no overlapping of molecules, but, owing to the small number of Fourier terms, most atoms were not resolved and false peaks near the iodine atom made it impossible to locate the acetate group. The *b*-axis projection, which was thus expected to show the molecule viewed side-on, gave still less resolution and indicated moreover a probable partial overlap of the molecules.

Attention was therefore focused on the *a*-axis projection as more likely to yield to interpretation. The second Fourier synthesis was computed, utilising additional terms from a

TABLE 1. *Comparison of the observed and calculated structure amplitudes for lanostenyl iodoacetate.*

hkl	$F_{obs.}$	$F_{calc.}$	*hkl*	$F_{obs.}$	$F_{calc.}$	*hkl*	$F_{obs.}$	$F_{calc.}$	*hkl*	$F_{obs.}$	$F_{calc.}$
000		+1256	026	19	+13	0,3,38	<20	−1	0,5,30	36	+40
002	80	−109	027	132	+151	0,3,39	21	+21	0,5,31	<20	+3
004	110	+151	028	23	+3	0,3,40	<20	+1	0,5,32	21	−30
006	144	−175	029	158	−142	0,3,41	20	−20	0,5,33	<20	0
008	151	+167	0,2,10	73	+80				0,5,34	<20	+13
0,0,10	140	−168	0,2,11	94	+98	040	125	−131	0,5,35	<20	0
0,0,12	220	+209	0,2,12	23	−22	041	105	+110	0,5,36	20	−20
0,0,14	157	−144	0,2,13	49	−76	042	104	+123			
0,0,16	61	+74	0,2,14	<15	+33	043	75	−78	060	51	+59
0,0,18	72	−64	0,2,15	26	+54	044	93	−98	061	46	+40
0,0,20	90	+69	0,2,16	30	−10	045	43	+55	062	68	−82
0,0,22	33	−21	0,2,17	43	−63	046	108	+85	063	80	−54
0,0,24	90	+72	0,2,18	<15	+13	047	30	−31	064	60	+77
0,0,26	<20	+5	0,2,19	73	+74	048	29	−30	065	24	+45
0,0,28	35	+20	0,2,20	<15	−18	049	174	+164	066	43	−58
0,0,30	<20	−3	0,2,21	16	−40	0,4,10	36	+42	067	93	−95
0,0,32	24	+9	0,2,22	17	+2	0,4,11	21	−41	068	61	+75
0,0,34	<20	+4	0,2,23	17	+26	0,4,12	153	−134	069	34	+54
0,0,36	36	+8	0,2,24	18	−24	0,4,13	30	+40	0,6,10	53	−54
0,0,38	<20	+8	0,2,25	<18	−21	0,4,14	68	+63	0,6,11	42	−38
0,0,40	23	−14	0,2,26	25	−6	0,4,15	77	−75	0,6,12	26	+48
			0,2,27	<20	+8	0,4,16	72	−65	0,6,13	<16	−2
011	76	+71	0,2,28	<20	−9	0,4,17	<18	+21	0,6,14	18	−40
012	17	+13	0,2,29	<20	−14	0,4,18	55	+44	0,6,15	32	−25
013	80	−74	0,2,30	28	−3	0,4,19	<18	−26	0,6,16	17	+42
014	102	−89	0,2,31	<20	−1	0,4,20	19	−24	0,6,17	44	+47
015	24	−26	0,2,32	<20	−2	0,4,21	<18	+23	0,6,18	22	−27
016	91	−80	0,2,33	<20	−5	0,4,22	19	+20	0,6,19	<18	−11
017	59	−56	0,2,34	<20	+9	0,4,23	29	−24	0,6,20	<18	+27
018	60	+63	0,2,35	38	−14	0,4,24	34	−29	0,6,21	30	+21
019	96	+86	0,2,36	<20	+2	0,4,25	35	+2	0,6,22	<20	−17
0,1,10	51	−54	0,2,37	<20	+9	0,4,26	18	+18	0,6,23	34	−25
0,1,11	<15	−10	0,2,38	20	−14	0,4,27	<18	+4	0,6,24	<20	+25
0,1,12	86	+87				0,4,28	20	−13	0,6,25	20	−6
0,1,13	42	+47	031	9	+9	0,4,29	<20	+8	0,6,26	24	−4
0,1,14	91	−85	032	23	+38	0,4,30	<20	−4	0,6,27	<20	−12
0,1,15	15	−23	033	91	+81	0,4,31	28	+12	0,6,28	<20	+14
0,1,16	49	+61	034	54	+48	0,4,32	<20	−4	0,6,29	32	+20
0,1,17	15	+27	035	66	−64	0,4,33	20	−8	0,6,30	<20	−14
0,1,18	95	−83	036	34	−36	0,4,34	<20	+6	0,6,31	<20	+2
0,1,19	91	−78	937	140	+93	0,4,35	<20	+2	0,6,32	<20	+4
0,1,20	73	+78	038	40	+43				0,6,33	20	−11
0,1,21	49	+52	039	36	−42	051	45	−26			
0,1,22	55	−46	0,3,10	42	+33	052	<16	+4	071	17	+8
0,1,23	21	−26	0,3,11	63	+65	053	<16	0	072	<16	+8
0,1,24	68	+65	0,3,12	50	+38	054	16	−21	073	34	−30
0,1,25	26	+35	0,3,13	63	−66	055	20	+5	074	16	+8
0,1,26	63	−53	0,3,14	74	−73	056	24	−32	075	<16	+24
0,1,27	28	−32	0,3,15	100	+94	057	56	−28	076	<16	+5
0,1,28	32	+43	0,3,16	36	+1	058	77	−54	077	17	−30
0,1,29	28	+27	0,3,17	72	−70	059	<18	−10	078	21	+21
0,1,30	37	−44	0,3,18	<18	−26	0,5,10	43	+44	079	<18	+14
0,1,31	34	−33	0,3,19	60	+70	0,5,11	76	−48	0,7,10	<18	+11
0,1,32	30	+40	0,3,20	<18	+7	0,5,12	71	−63	0,7,11	<18	−4
0,1,33	<20	+15	0,3,21	45	−56	0,5,13	24	−27	0,7,12	21	+9
0,1,34	<20	−14	0,3,22	<18	−7	0,5,14	18	+24	0,7,13	56	+59
0,1,35	20	−15	0,3,23	76	+78	0,5,15	42	−30	0,7,14	21	−16
0,1,36	<20	+24	0,3,24	21	+21	0,5,16	21	−29	0,7,15	<18	−35
0,1,37	28	+26	0,3,25	41	−51	0,5,17	<18	−1	0,7,16	18	+8
0,1,38	<20	−4	0,3,26	30	−30	0,5,18	71	+70	0,7,17	32	+44
0,1,39	21	−20	0,3,27	67	+60	0,5,19	<18	−5	0,7,18	<20	−10
0,1,40	<20	+8	0,3,28	<20	+8	0,5,20	22	−29	0,7,19	21	−36
0,1,41	<20	+10	0,3,29	21	−31	0,5,21	18	−4	0,7,20	<20	+13
0,1,42	20	−16	0,3,30	25	−22	0,5,22	37	+47	0,7,21	33	+40
			0,3,31	34	+40	0,5,23	<18	−4	0,7,22	21	−21
020	62	−71	0,3,32	20	+15	0,5,24	30	−43	0,7,23	24	−36
021	47	−53	0,3,33	30	−34	0,5,25	28	−27	0,7,24	<20	+11
022	23	+4	0,3,34	23	−17	0,5,26	19	+29	0,7,25	21	+34
023	49	+50	0,3,35	30	+34	0,5,27	29	−24	0,7,26	<20	−10
024	256	−236	0,3,36	<20	+10	0,5,28	30	−35	0,7,27	20	−37
025	292	−299	0,3,37	21	−24	0,5,29	<20	+3	0,7,28	<20	+10

TABLE 1. (*Continued.*)

hkl	$F_{obs.}$	$F_{calc.}$	*hkl*	$F_{obs.}$	$F_{calc.}$	*hkl*	$F_{obs.}$	$F_{calc.}$	*hkl*	$F_{obs.}$	$F_{calc.}$
0,7,29	20	+26	101	69	+73	2,0,24	<18	+20	4,0,11	41	−47
0,7,30	<20	+7	102	<10	−4	2,0,25	29	−33	4,0,12	<18	−3
0,7,31	20	−18	103	201	+173	2,0,26	<20	+20	4,0,13	23	−35
			104	44	+25	2,0,27	<20	−29	4,0,14	33	+24
080	27	+19	105	184	+153	2,0,28	<20	0	4,0,15	24	−40
081	<18	−40	106	94	−52	2,0,29	33	−37	4,0,16	<18	−4
082	25	−22	107	129	+117				4,0,17	42	−49
083	66	+71	108	41	−44	301	88	+79	4,0,18	<20	−1
084	<18	+11	109	153	+158	302	<15	−7	4,0,19	32	−51
085	28	−48	1,0,10	54	−46	303	61	+70	4,0,20	<20	−10
086	<18	−4	1,0,11	70	+102	304	59	−52	4,0,21	25	−31
087	32	+50	1,0,12	15	−20	305	92	+70	4,0,22	<20	−7
088	<18	−3	1,0,13	62	+89	306	<15	−18	4,0,23	36	−53
089	<18	−34	1,0,14	35	−46	307	49	+41	4,0,24	<20	−4
0,8,10	19	−23	1,0,15	102	+113	308	56	+26	4,0,25	<20	−34
0,8,11	<20	+40	1,0,16	18	−37	309	28	+35	4,0,26	<20	+5
0,8,21	<20	+18	1,0,17	18	+37	3,0,10	24	−23	4,0,27	27	−35
0,8,13	20	−42	1,0,18	35	−25	3,0,11	119	+89	4,0,28	<20	−5
0,8,14	<20	−23	1,0,19	49	+58	3,0,12	93	−83	4,0,29	<20	−10
0,8,15	21	+31	1,0,20	54	−54	3,0,13	<16	+18	4,0,30	<20	+2
0,8,16	20	+15	1,0,21	44	+55	3,0,14	80	−76	4,0,31	27	−33
0,8,17	<20	−24	1,0,22	31	−29	3,0,15	33	+27			
0,8,18	27	−15	1,0,23	29	+29	3,0,16	24	−48	501	<18	−22
0,8,19	<20	+24	1,0,24	41	−43	3,0,17	26	+23	502	<18	+2
0,8,20	<20	−4	1,0,25	<20	+18	3,0,18	51	−58	503	<18	−22
0,8,21	<20	−10	1,0,26	29	−26	3,0,19	<18	+20	504	28	−23
0,8,22	20	−12				3,0,20	24	−46	505	34	−39
			200	48	+80	3,0,21	<18	+20	506	<18	−10
091	29	+11	201	<10	+23	3,0,22	21	−29	507	<18	−28
092	<20	0	202	87	+82	3,0,23	<18	+10	508	<18	−15
093	30	+30	203	11	+8	3,0,24	41	−50	509	32	−24
094	<20	−3	204	150	+118	3,0,25	25	+20	5,0,10	33	−30
095	20	+7	205	61	−53	3,0,26	41	−49	5,0,11	<20	−23
096	<20	−8	206	68	+84	3,0,27	<20	+1	5,0,12	<20	−32
097	<20	−4	207	78	−60	3,0,28	43	−50	5,0,13	<20	−20
098	<20	+15	208	123	+108	3,0,29	<20	+11	5,0,14	<20	−22
099	20	−15	209	72	−59	3,0,30	40	−44	5,0,15	25	−17
0,9,10	20	−26	2,0,10	50	+55	3,0,31	<20	−17			
0,9,11	20	+13	2,0,11	21	−42	3,0,32	23	−22	600	<20	−23
0,9,12	<20	+27	2,0,12	56	+77				601	35	−22
0,9,13	20	−13	2,0,13	18	+6	400	<15	−13	602	55	−57
			2,0,14	38	+52	401	54	+25	603	39	−22
0,10,0	<20	−36	2,0,15	64	−66	402	17	−4	604	<20	−19
0,10,2	24	+45	2,0,16	<16	+25	403	53	−35			
0,10,4	<20	−32	2,0,17	<16	−30	404	<15	−19	701	<20	−22
0,10,6	32	+46	2,0,18	17	+42	405	17	−10	702	<20	+7
0,10,8	20	−36	2,0,19	37	−59	406	35	−17	703	<20	−24
0,10,10	23	+32	2,0,20	31	+39	407	65	−59	704	<20	−4
			3,0,21	35	−44	408	<16	−5	705	24	−33
0,11,1	20	−21	2,0,22	19	+28	409	38	−37			
0,11,3	20	+6	2,0,23	<18	−26	4,0,10	34	−30			

TABLE 2. *Atomic parameters*

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
I	0·064	−0·095	0·258	$C_{(10)}$	0·500	0·289	0·086	$C_{(22)}$	0·658	0·564	0·078
$O_{(1)}$	0·372	0·184	0·261	$C_{(11)}$	0·317	0·356	0·076	$C_{(23)}$	0·511	0·564	−0·042
$O_{(2)}$	0·400	0·061	0·217	$C_{(12)}$	0·333	0·461	0·044	$C_{(24)}$	0·320	0·600	−0·036
$C_{(1)}$	0·589	0·103	0·165	$C_{(13)}$	0·506	0·466	0·025	$C_{(25)}$	0·634	0·667	−0·060
$C_{(2)}$	0·432	0·131	0·189	$C_{(14)}$	0·667	0·483	0·050	$C_{(26)}$	0·556	0·678	−0·097
$C_{(3)}$	0·267	0·131	0·167	$C_{(15)}$	0·855	0·489	0·035	$C_{(27)}$	0·661	0·758	−0·117
$C_{(4)}$	0·286	0·222	0·138	$C_{(16)}$	0·816	0·567	−0·001	$C_{(28)}$	0·645	0·767	−0·153
$C_{(5)}$	0·464	0·214	0·117	$C_{(17)}$	0·600	0·555	−0·004	$C_{(29)}$	0·767	0·865	−0·175
$C_{(6)}$	0·603	0·189	0·139	$C_{(18)}$	0·600	−0·033	0·158	$C_{(30)}$	0·467	0·842	−0·164
$C_{(7)}$	0·765	0·186	0·114	$C_{(19)}$	0·753	0·111	0·189	$C_{(31)}$	0·300	−0·017	0·267
$C_{(8)}$	0·789	0·308	0·094	$C_{(20)}$	0·442	0·117	0·092	$C_{(32)}$	0·342	0·095	0·244
$C_{(9)}$	0·634	0·372	0·079	$C_{(21)}$	0·542	0·350	0·003				

TABLE 3. *Intramolecular bond lengths and intermolecular approach distances.*

(a) *Intramolecular bond lengths.*

	Å		Å		Å		Å
I–$C_{(31)}$	2·02	$C_{(4)}$–$C_{(5)}$	1·57	$C_{(11)}$–$C_{(12)}$	1·69	$C_{(17)}$–$C_{(23)}$	1·59
$C_{(31)}$–$C_{(32)}$	1·52	$C_{(5)}$–$C_{(6)}$	1·39	$C_{(12)}$–$C_{(13)}$	1·51	$C_{(23)}$–$C_{(24)}$	1·52
$C_{(32)}$–$O_{(1)}$	1·19	$C_{(5)}$–$C_{(20)}$	1·44	$C_{(13)}$–$C_{(14)}$	1·56	$C_{(23)}$–$C_{(25)}$	1·62
$C_{(32)}$–$O_{(2)}$	1·24	$C_{(6)}$–$C_{(7)}$	1·54	$C_{(14)}$–$C_{(9)}$	1·67	$C_{(25)}$–$C_{(26)}$	1·56
$C_{(2)}$–$O_{(2)}$	1·33	$C_{(6)}$–$C_{(1)}$	1·39	$C_{(13)}$–$C_{(21)}$	1·55	$C_{(26)}$–$C_{(27)}$	1·40
$C_{(1)}$–$C_{(2)}$	1·53	$C_{(7)}$–$C_{(8)}$	1·54	$C_{(14)}$–$C_{(22)}$	1·39	$C_{(27)}$–$C_{(28)}$	1·41
$C_{(1)}$–$C_{(18)}$	1·51	$C_{(8)}$–$C_{(9)}$	1·50	$C_{(14)}$–$C_{(13)}$	1·56	$C_{(28)}$–$C_{(29)}$	1·64
$C_{(1)}$–$C_{(19)}$	1·55	$C_{(9)}$–$C_{(10)}$	1·38	$C_{(15)}$–$C_{(16)}$	1·66	$C_{(28)}$–$C_{(30)}$	1·64
$C_{(2)}$–$C_{(3)}$	1·52	$C_{(10)}$–$C_{(5)}$	1·47	$C_{(16)}$–$C_{(17)}$	1·66		
$C_{(3)}$–$C_{(4)}$	1·52	$C_{(10)}$–$C_{(11)}$	1·61	$C_{(17)}$–$C_{(13)}$	1·64		

Mean C–C: 1·54 ± 0·09 Å.

(b) *Intermolecular approach distances.*

	Å		Å		Å		Å
I–$O_{(1)}$	5·7	$C_{(20)}$–$C_{(23)}$	5·0	$C_{(32)}$–$C_{(29)}$	3·9	$C_{(18)}$–$C_{(27)}$	5·1
$O_{(1)}$–$C_{(30)}$	3·9	$C_{(31)}$–$C_{(30)}$	4·0	$C_{(22)}$–$C_{(27)}$	4·5	$C_{(18)}$–$C_{(26)}$	4·4
$C_{(28)}$–$C_{(18)}$	4·8	$C_{(26)}$–$C_{(24)}$	4·2	$C_{(22)}$–$C_{(26)}$	5·4	$C_{(31)}$–$C_{(29)}$	5·0
$C_{(21)}$–$C_{(21)}$	4·4	$C_{(32)}$–$C_{(30)}$	4·4	$C_{(22)}$–$C_{(28)}$	5·0		

120-hour moving-film exposure, the signs being fixed by the iodine atom contribution. This distribution showed improved resolution but still did not permit location of the acetate group for the following reasons: (1) the number of peaks adjacent to the iodine atom was greater than necessary to account for the acetate group; (2) the inability to obtain accurate cell dimensions, owing to the large temperature factor, made it necessary to keep in mind the possibility that a molecule of the solvent might be included in the structure adjacent to the iodine atom;

FIG. 1. *Partial difference synthesis, $\rho(z)$–$\rho_1(z)$.*

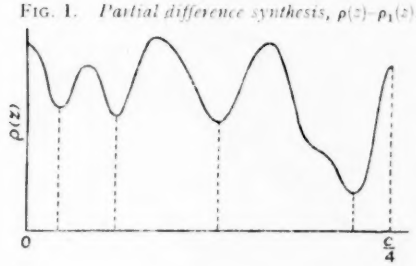
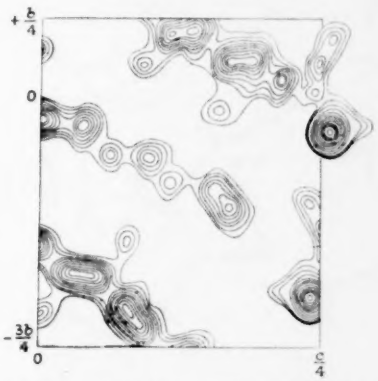


FIG. 2. *The final electron-density distribution projected on* (100).



Contours for the iodine atom are drawn at intervals of 5 eA^{-2} and for other atoms at 1 eA^{-2}. The lowest contour value shown is 2 eA^{-2}.

(3) both ends of the ridge were adjacent to iodine atoms and there was no distinctive indication at this stage about which end of the ridge (molecule) the acetate group was related to.

It was therefore clear that progress in the analysis would be prevented until the acetate group was located. This problem was resolved by computing the uni-dimensional Fourier synthesis $\rho(z)$ (Fig. 1, with the iodine atom removed) and evaluating the number of atoms at different levels. This revealed that there could be only three atoms (of the asymmetric unit) near the level $z = 0{\cdot}25$ and that there was none or at most only one atom in the region $z = 0{\cdot}225$. Hence, with the known bond-lengths and angles of the iodoacetate group and account being taken of the electron-density distribution near the iodine atom in the *b*-axis projection, the number of sterically possible positions of the acetate group was reduced. When the acetate group was located in space, this determined which end of the ridge corresponded to the ring

system since it was known that the acetate group was directly linked to ring A. Furthermore, it was then apparent that the other end of the ridge must correspond to the side chain. Succes-

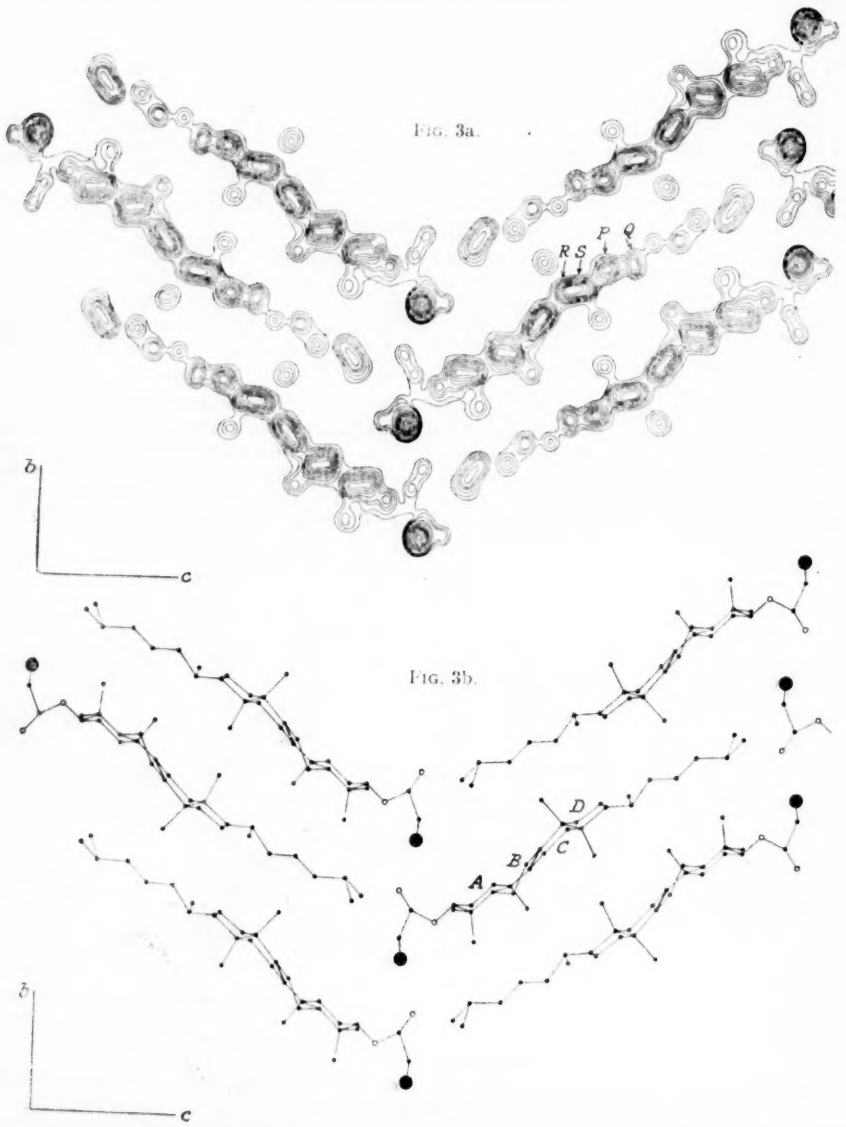


FIG. 3a. *The electron-density distribution, $\rho(y, z)$, extended over several unit cells to illustrate the molecular packing in the crystal. The penultimate electron-density distribution was used to compose this figure, and thus the contour distribution differs slightly from that of Fig. 2.*

FIG. 3b. *The corresponding diagram of the crystal structure.*

sive trial models for the molecule were fitted to the projection, and structure amplitudes calculated. Since the molecular models could not deviate far from the region indicated by the ridge but merely differ in minor details, the calculation of structure amplitudes (at this stage, the reliability factor, $R = \Sigma|F_o - F_c|/\Sigma|F_o| = 0{\cdot}38$) permitted some additional signs to be fixed. By

repeated Fourier syntheses, the reliability factor for this projection was reduced to 0·25 and the main outlines of the structure, *i.e.*, location of the ring system, disposition of the side methyl groups, and the configuration of the side chain became more evident.

Since the y and z co-ordinates of all atoms were thus fixed with reasonable accuracy, it was possible to return to the interpretation of the b-axis projection in order to determine the x co-ordinates and to confirm some points of the structure which could not be decisively derived from the a-axis projection alone since this presented only an edge-on view of the molecule. By

FIG. 4a.

FIG. 4b.

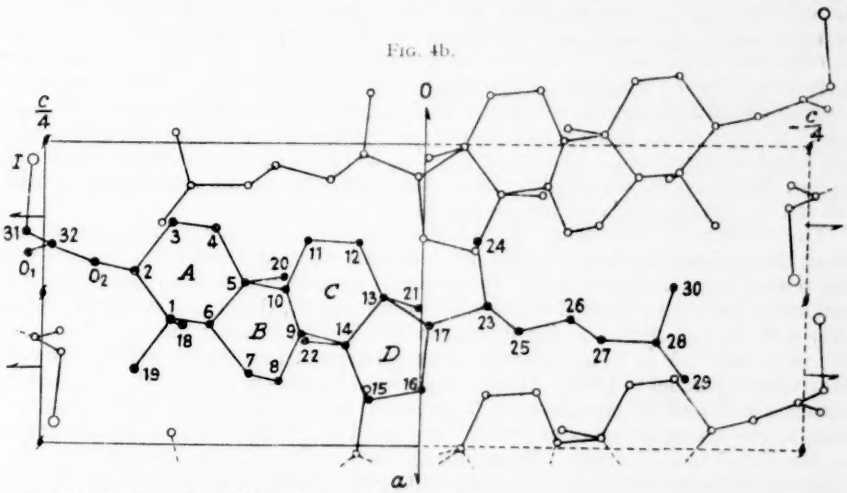


FIG. 4a. *The electron-density distribution projected on* (010).
FIG. 4b. *The corresponding diagram of the crystal structure. The molecule* (i.e. *the asymmetric unit*) *is shown in thick lines while parts of two related molecules appear in thinner lines.*

utilising nearly all the *h*0*l* structure amplitude terms available, Fourier synthesis yielded the electron-density distribution $\rho(x, z)$ on which all atomic positions could be reasonably located, although individual atoms were not all resolved. Two consecutive refinements reduced the reliability factor from 0·35 to 0·25 and thus confirmed the structure derived from the a-axis projection.

By making minor adjustments in atomic parameters indicated by a comparison of the two projections, the reliability factors were reduced finally to 0·21 and 0·22 for the 0*kl* and *h*0*l* structure amplitudes respectively (Table 1). The final contour map of the a-axis projection is shown in Fig. 2, a similar projection extending over several unit cells in Fig. 3a with the corresponding molecular diagram in Fig. 3b. This shows the packing of molecules in the crystal. The contour map of electron density projected down the b axis is shown in Fig. 4a, with an interpretive diagram in Fig. 4b.

The parameters of all 35 atoms of the asymmetric unit (molecule) are listed in Table 2, the origin being the same as that given for space group $P2_12_12_1$ in "International Tables" (*loc. cit.*). The atoms $C_{(1)}$ to $C_{(30)}$ are numbered as for triterpenes [see (I) and Fig. 4b]. The intramolecular bond lengths calculated from these parameters are given in Table 3 with a selection of the smaller intermolecular approach distances.

Discussion

The resolution of atoms obtained in this analysis is less than can be achieved for smaller molecules, mainly owing to the large temperature factor restricting the number of observed reflections. As a result, the bond lengths can be quoted only to within 0·09 Å, but are sufficiently precise to define adequately the structure and stereochemistry of lanostenyl iodoacetate and hence of lanostenol provided that there is no inversion. The approach distances between molecules correspond to van der Waals bonds.

The existence of the double bond in the molecules between $C_{(9)}$ and $C_{(10)}$ can be deduced from the two projections independently of any chemical evidence, thus the planarity of $C_{(5)}$, $C_{(8)}$, $C_{(9)}$, $C_{(10)}$, $C_{(11)}$, and $C_{(18)}$, associated with the double bond modifies the regular zig-zag which would be expected in a fully hydrogenated *trans*-fused ring system. This aspect is clearly shown in Figs. 3a and b. In the second projection, the angular disposition of the group $C_{(5)}$–$C_{(14)}$ associated with the double bond is revealed in Figs. 4a and b. If no strain were involved, this double bond would confer a symmetrical relationship on rings B and C in that $C_{(7)}$ would be symmetrically disposed with respect to $C_{(12)}$ and $C_{(6)}$ to $C_{(13)}$ across the centre of the double bond. However, it was noted in the *b*-axis projection particularly that $C_{(12)}$ was displaced from the expected position (compare the projected distances $C_{(7)}$–$C_{(8)}$ and $C_{(11)}$–$C_{(12)}$). Consideration of a simple ball-and-rod model showed that the observed displacement of $C_{(12)}$ was in agreement with the shift produced as a result of the fusion of the five-membered ring D to the six-membered ring C. The *trans*-fusion C–D involved considerable strain, which was partially relieved by the movement of $C_{(12)}$. Although a minor point, this was satisfactory confirmation of the correctness of the structure which had been deduced. The bonds $C_{(1)}$–$C_{(18)}$ and $C_{(5)}$–$C_{(20)}$ should lie parallel if ring A is regular, but there is considerable steric hindrance between the methyl groups which is relieved by a lateral displacement (see Fig. 3).

The evidence for the linkage of the side chain to the ring system at $C_{(17)}$ is as follows. When the analysis was being carried out, chemical evidence could not determine whether ring D was six- or five-membered. In the *a*-axis projection, it is clear that if ring D is six-membered, then the projected distance between [$C_{(16)}$, $C_{(17)}$] and $C_{(23)}$ should be approximately 0·90 Å., *i.e.*, similar in distribution to *RS* (Fig. 3), whereas the observed value *i.e.*, *PQ*, is at least 1·5 Å. This distance must correspond to a single carbon–carbon bond, lying almost parallel to (100). Hence ring D must be five-membered, the ring system terminating at *P*, and the two atoms at *Q* (indicated by the peak height in the contour map) must lie one above the other and must correspond to the first atom of the side chain with an associated methyl group. From this projection, it could be inferred that the side chain was attached to $C_{(16)}$ or $C_{(17)}$, but could not possibly be associated with $C_{(15)}$. Consideration of the *b*-axis projection revealed that the point of linkage is $C_{(17)}$ (cf. Fig. 4).

The structural formula deduced for lanostenol in the present study is given by (I). The arrangement of (I) has been brought into line with those of the steroids; this is contrary to the convention for triterpenoids, but the latter appears to have outlived its convenience and will cause confusion when the stereochemistry of the compounds is to be compared with that of the steroids for which a widely-used standardisation has been achieved (Fieser and Fieser, "Natural Products related to Phenanthrene," Reinhold, New York, 1949; *J.*, 1951, 3532). Halsall, Jones, and Meakins (*J.*, 1952, 2862) have made a similar modification. The numbering for triterpenoids has been preserved, however, to prevent confusion, but the stereochemistry of lanostenol has been based on the convention accepted for steroids (*loc. cit.*).

The molecule of lanostenol, like those of many steroids (Bernal, Crowfoot, and Fankuchen, *Trans. Roy. Soc.*, 1940, *A*, **239**, 135), is flat and lath-shaped, of dimensions 20 × 6 × 5 Å.

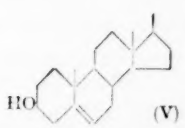
Ring A (cf. Fig. 3) is of the "chair" or "Z" type, ring B is *trans*-fused to ring A, while

rings B and C share the double bond $C_{(9)}$–$C_{(10)}$ which imposes planarity on the atoms $C_{(5)}$···$C_{(14)}$. The general disposition of the composite B–C ring system is of " chair " type with atoms $C_{(6)}$ and $C_{(7)}$ above and $C_{(12)}$ and $C_{(13)}$ below the plane $C_{(5)}$···$C_{(14)}$. This is shown in Fig. 3. Rings C–D are *trans*-fused. Because rings A–B are *trans*-fused, the relation of the $C_{(5)}$-methyl group is fixed and is considered as β-oriented (Fiesers' notation). The hydroxyl group is attached to $C_{(2)}$ and is β-oriented or equatorial (Barton, *Experientia*, 1950, **6**, 376). The $C_{(18)}$–$C_{(19)}$-*gem*-dimethyl group is adjacent to the hydroxyl group; this agrees with chemical evidence. The $C_{(13)}$- and $C_{(14)}$-methyl groups are β- and α-oriented, respectively, the bonds, $C_{(13)}$–$C_{(14)}$ and $C_{(14)}$–$C_{(22)}$, being non-parallel, owing to the distortion imposed by the *trans*-fusion of C–D. The side chain is β-oriented with respect to $C_{(17)}$. The disposition of the side chain is such as to bring $C_{(24)}$, $C_{(29)}$, and $C_{(30)}$ approximately coplanar with the ring system, leaving only the four methyl groups at $C_{(18)}$, $C_{(20)}$, $C_{(21)}$ and $C_{(22)}$ projecting from the general plane of the molecule.

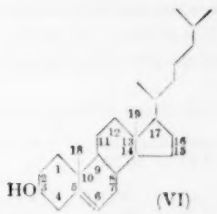
The equatorial position of the ring-A hydroxyl group and the " chair " configuration of this ring are in accord with the generally accepted view (Barton, *loc. cit.*; Hassel, *Research*, 1950, **3**, 504) that these dispositions are more stable than the polar position of the bond or the movable " boat " formation of the ring. In addition, it appears that when two rings are fused through a double bond the composite ring system in a " chair " form is more stable than one of a boat formation. A model of the lanostenol molecule is shown in Fig. 4b.

The structural formula for lanostenol is in agreement with the partial formula proposed recently by Ruzicka *et al.* (*loc. cit.*) and Barton, McGhie, *et al.* (*loc. cit.*), based on chemical evidence and study of the infra-red and ultra-violet spectra of derivatives. The *X*-ray analysis has however determined unambiguously the point of linkage of the side chain to the ring system and has provided a complete description of the stereochemistry, independently of chemical evidence.

Lanostadienol (II) differs from lanostenol only in the existence of a $C_{(27)}$–$C_{(28)}$ reactive double bond and can therefore be assumed to have the same configuration as lanostenol with only a minor steric modification of the side chain. All chemical evidence points to agnostadienol (III) and agnostatrienol (IV) having the same structural skeleton, which will therefore be similar to that of lanostenol, apart from steric modifications due to the presence of the two inert double bonds and the consequent planarity of the adjacent atoms.



(V)



(VI)

The skeleton of the wool-wax triterpenes bears a close resemblance to the steroid nucleus (V) (except for the position of the double bond) while the position of the hydroxyl group and of $C_{(5)}$ (steroid $C_{(10)}$) and of $C_{(13)}$ (steroid $C_{(13)}$)-methyl groups are the same. In addition, the side chain is attached to $C_{(17)}$ in both steroids and triterpenoids. Comparison of Fig. 4b with Carlisle and Crowfoot's model of cholesterol (VI) (*loc. cit.*, Fig. 10) reveals a striking similarity. Lanostenol differs structurally from cholesterol only in the position of the double bond and in the addition of the three methyl groups, at $C_{(18)}$, $C_{(19)}$, and $C_{(22)}$. There was, however, no similarity in the crystalline forms, cholesteryl iodide being monoclinic and lanostenyl iodoacetate orthorhombic.

The authors thank Mr. R. G. Curtis of the Organic Chemistry Section for many helpful discussions regarding the chemistry of lanostenol.

CHEMICAL PHYSICS SECTION, DIVISION OF INDUSTRIAL CHEMISTRY,
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445. *The Reaction between Organic Hydroperoxides and Iodide in the Presence of Iron Salts.*

By W. S. Wise and G. H. Twigg.

The reaction between iodide ions and organic hydroperoxides is catalysed by iron salts. With αα-dimethylbenzyl and *tert.*-butyl hydroperoxides, the mechanism involves the alternate oxidation and reduction of the iron :

$$Fe^{2+} + R{\cdot}O{\cdot}OH \longrightarrow Fe^{3+} + RO\cdot + OH^-$$
$$Fe_3^+ + I^- \longrightarrow (FeI)^{2+} \longrightarrow Fe^{2+} + \tfrac{1}{2}I_2$$

For αα-dimethylbenzyl hydroperoxide, the results yield a value for the rate constant of the first reaction, which is in agreement with the known value.

Although the catalysis of the reaction between iodide ions and peroxides by tungstic or molybdic acid has long been known (Brode, *Z. physikal. Chem.*, 1901, **37**, 257), the mechanism has not apparently been investigated in terms of free radicals. In the present investigation, iron salts were used as a catalyst for the reaction of organic hydroperoxides with iodide. The iron solution was added to a mixture of peroxide, iodide, and acid through which a stream of nitrogen was passed. The liberated iodine was continuously titrated by addition of sodium thiosulphate from a burette. Preliminary experiments showed that the rate of disappearance of thiosulphate was unaffected by the rate of addition from the burette, even in moderately acid solutions. The reaction rate was the same in the dark, in diffuse daylight, or when a " Photoflood " lamp shone close to the reaction vessel. All experiments were therefore carried out in diffuse daylight.

Stoicheiometry and Products of Reaction.—In a large number of experiments under a variety of conditions it was found that the total amount of iodine liberated was given by $I_2 \equiv RO_2H$ within an accuracy of about 2% for αα-dimethylbenzyl and *tert.*-butyl hydroperoxides in the absence of oxygen. In the presence of oxygen, the amount of iodine liberated was considerably greater—roughly twice that equivalent to the hydroperoxide when the mixture was kept saturated with oxygen. In view of this complication, the experiments were carried out in nitrogen. With *tert.*-amyl and tetrahydronaphthyl hydroperoxides the amount of iodine liberated was less than the stoicheiometric amount when the reaction was carried out in the absence of oxygen, as shown in Table 1.

Table 1. *Liberation of iodine by* tert.*-amyl and tetrahydronaphthyl hydroperoxides.*

tert.-Amyl peroxide : initial concn., $3{\cdot}16 \times 10^{-3}$M.			Tetrahydronaphthyl peroxide : initial concn., $2{\cdot}0 \times 10^{-3}$M.		
[Catalyst]/[RO_2H], initial	[I^-]/[RO_2H], initial	Iodine liberated, % of theory	[Catalyst]/[RO_2H], initial	[I^-]/[RO_2H], initial	Iodine liberated, % of theory
0·075	60	64	0·12	50	19
0·038	60	85	0·24	50	17
0·075	150	79	0·60	50	15
0·038	150	91	1·20	50	13
0·075	300	87	0·60	250	21
0·038	300	92	0	300	83

These results show that the catalysed reaction with iodide is not suitable for estimating peroxides in general, although for αα-dimethylbenzyl and *tert.*-butyl hydroperoxides it affords an extremely convenient method of estimation for aqueous solutions (see preceding paper). The product of the peroxide decomposition was found to be 2-phenylpropan-2-ol from αα-dimethylbenzyl hydroperoxide, and *tert.*-butyl alcohol from *tert.*-butyl hydroperoxide (see p. 2171).

Factors affecting Catalysis.—The effect of adding fluoride is to stop the catalysis, no more iodine being liberated. The rate of reaction is decreased slightly by increasing the amount of sulphuric acid present, but is very nearly independent of acid concentration in a

perchloric acid medium free from sulphate ions. Other things being equal, the rate of reaction is about 20% greater in the perchloric acid medium. There is a very slight increase in the rate when the perchloric acid concentration is increased, probably owing to the well-known equilibrium :

$$Fe^{3+} + H_2O \rightleftharpoons Fe(OH)^{2+} + H^+$$

The addition of concentrated sodium sulphate solution decreased the rate to about 10% of its normal value; this, taken in conjunction with the above results, suggests that the complexes formed between ferric ions and sulphate ions react more slowly with iodide than do ferric ions. If insufficient acid is present the alkali formed during the reaction eventually causes precipitation of ferric ions, stopping the reaction. The above evidence leaves no doubt that the reduction of ferric ions to ferrous ions is concerned in the catalysis.

The Reaction with Excess of Ferrous Ions in the Presence of Fluoride.—Although the addition of fluoride stops the catalysis, it is possible to investigate the reaction in the presence of fluoride when an excess of ferrous ions over peroxide is added. Preliminary experiments showed that a large excess of fluoride (~100-fold) was then required to eliminate the catalysis. If the peroxide was added to a mixture of ferrous ions and fluoride, no iodine was liberated. If, on the other hand, the ferrous solution was added to a mixture of peroxide and fluoride, some iodine was produced. Experiments were therefore carried out in which the ferrous solution was added slowly and continuously to the reaction mixture containing excess of fluoride. The total amount of iodine liberated was obtained by titration with thiosulphate. The residual ferrous ion was estimated by the 2 : 2′-dipyridyl method. Typical results for αα-dimethylbenzyl hydroperoxide are shown in Table 2. It will be observed that the sum of the iodine liberated and the ferrous ion

TABLE 2. *Iodine liberation and ferrous-ion consumption in presence of fluoride.*

Rate of addition of ferrous ion : 10^{-5} mole/l./min.	4·7	18·8	47
Moles of I_2 liberated per mole of RO_2H	0·39	0·25	0·14
Moles of Fe^{2+} oxidised per mole of RO_2H	1·07	1·23	1·33
Sum of previous two lines	1·46	1·48	1·47

oxidised per mole of peroxide is constant at about 1·5. Similar results were obtained for tetrahydronaphthyl hydroperoxide.

Mechanism of the Reaction.—The above results indicate that the mechanism of the catalysis is the alternate oxidation of ferrous ions :

$$Fe^{2+} + RO_2H \longrightarrow Fe^{3+} + RO\cdot + OH^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

and the reduction of ferric ions by iodide :

$$Fe^{3+} + I^- = Fe^{2+} + \tfrac{1}{2}I_2$$

The mechanism of the latter reaction is rather complicated (Fudge and Sykes, *J.*, 1952, 119); hence it is not easy to suggest a complete kinetic scheme for the catalysis.

The fluoride experiments (Table 2) suggest that, as the ferrous-ion concentration decreases, the amount of iodine liberated tends to one-half of that equivalent to the peroxide present. This would be expected if, in the absence of fluoride, one-half of the iodine liberated came from the ferric ions produced by reaction (1) (this step being now blocked by the fluoride) and the other half from the RO· radicals by a mechanism not involving ferric ions :

$$RO\cdot + I^- \longrightarrow RO^- + I\cdot \qquad\qquad 2I\cdot \longrightarrow I_2$$

In the presence of fluoride at higher ferrous-ion concentrations, the amount of iodine liberated tends to zero. This is explained if either the RO· radicals or species produced by them oxidise ferrous ions to ferric ions which cannot liberate iodine because of the fluoride present. The obvious reaction :

$$Fe^{2+} + RO\cdot \longrightarrow Fe^{3+} + RO^- \qquad\qquad RO^- + H^+ \longrightarrow ROH$$

has been shown in the preceding paper to be unlikely to occur in these conditions. This leaves as a possibility: $Fe^{2+} + I\cdot \longrightarrow FeI^{2+}$ (using Fudge and Sykes's reaction). The complex FeI^{2+} ultimately reacts in the presence of fluoride: $FeI^{2+} \longrightarrow Fe^{3+} + I^-$.

The rate constant of reaction (1) can be obtained from the catalytic experiments by making certain assumptions. The first is that at high iodide concentrations the rate of reaction becomes limited by the rate of reaction (1), *i.e.*, the reaction of iodide is fast enough to keep the iron salts mostly in the ferrous state; and the second is that the amount of iodine liberated is equivalent to the peroxide consumed, *i.e.*, that the concentration of transient species, such as I_2^-, is small compared with the concentrations of reactants. We then have that the rate of peroxide disappearance is given by $-dp/dt = k_1 p x_0 + k'[I^-]p$ where x_0 is the total concentration of iron salts present and k' is the rate of the uncatalysed reaction between iodide and peroxide.

From the graph of log p against t (Fig. 1) values of $(k_1 x_0 + k'[I^-])$ were obtained. It will be seen that good linear plots were obtained even at low iodide concentrations,

FIG. 1.

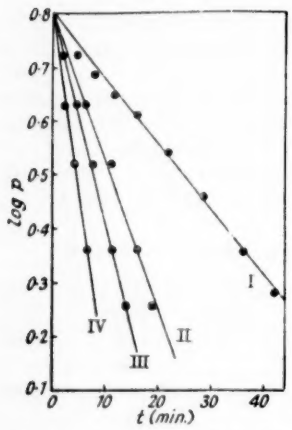

FIG. 2.

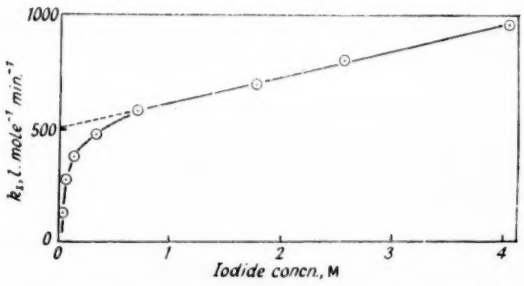

FIG. 1. *Graph of log* p *against time for various iodide concentrations. Curves* I—IV, 0·0325, 0·065, 0·131, *and* 0·330M, *respectively. Iron salt concentration was* $2·3 \times 10^{-4}$M.

FIG. 2. *Graph of the apparent value of* k_1 *against iodide concentration.*

although the slope varies with the iodide concentration. Fig. 2 shows the apparent value of k_1 as a function of the iodide concentration. The value of k' was found in separate experiments to be given under the present conditions by $k' = 1·1 \times 10^{12}\exp\{-15{,}200/\boldsymbol{R}T\}$ l. mole^{-1} min.$^{-1}$.

As expected, the value of k_1 changes as the iodide concentration increases, at first increasing rapidly and then more slowly. The increase at high iodide concentrations is apparently due to salt effects. The extrapolation shown to zero salt concentration, however, gives a value for k_1 of 510 l. mole^{-1} min.$^{-1}$, which compares satisfactorily with the value of 485 calculated from Fordham and Williams's results (*J. Amer. Chem. Soc.*, 1951, **73**, 1634).

The results with *tert.*-amyl and tetrahydronaphthyl hydroperoxides are more complicated owing to the participation of other reactions. The fact that the total amount of iodine liberated is less than the stoicheiometric amount is explained for *tert.*-amyl hydroperoxide by the greater instability of the RO· radical: $CMe_2Et\cdot O\cdot \longrightarrow COMe_2 + Et\cdot$. The ethyl radical may disappear without liberating iodine, *e.g.*, by reaction with hydroperoxide, $Et\cdot + RO\cdot OH \longrightarrow RO\cdot + EtOH$, or it may, as suggested by Merz and Waters (*J.*, 1949, S 15), react with the iodine already liberated.

With tetralin hydroperoxide there is a catalytic decomposition by ferrous ions in the absence of iodide. If this catalytic decomposition is significant in the presence of iodide,

the amount of iodine liberated would be less than that equivalent to the peroxide, as was found experimentally. There are two possible explanations of this catalytic decomposition: (i) that the RO· radical causes a catalytic decomposition of the peroxide to α-tetralone, being itself regenerated; (ii) that ferrous ions are regenerated from ferric ions by reaction with RO· radicals: $>CH{-}O{-} + Fe^{3+} \longrightarrow >C{=}O + Fe^{2+} + H^{+}$. In favour of this type of reaction is the fact that a mixture of ferrous ions and tetrahydronaphthyl hydroperoxide will reduce mercuric ions.

A kinetic examination of these two possibilities has shown that scheme (ii) is the more probable. With scheme (i) the ratio of iodine liberated to peroxide consumed should increase with iodide concentration, but should be independent of the ferrous-ion concentration, and in the absence of ferrous ions the same ratio should be found. For scheme (ii), again, it is found that the amount of iodine liberated increases as the iodide concentration is increased, but it decreases as the catalyst concentration is increased. This fits qualitatively the results shown in Table 1.

Experimental

Catalysed Iodide Reaction.—50 Ml. of aqueous peroxide solution (1 g./l. in most cases), 2 ml. of 10N-sulphuric acid, and 2—25 ml. of 50% sodium iodide, made up to a volume of 150 ml. with doubly distilled water, were placed in a flask contained in a thermostat. Nitrogen was bubbled through the mixture. The reaction was started by adding 1 ml. of ferrous sulphate solution (10 g./l. of $FeSO_4,7H_2O$), and the liberated iodine was titrated continuously with 0·1N-sodium thiosulphate from a burette. In the experiments shown in Fig. 2, the solution was made 0·1N in perchloric acid, and the catalyst solution was ferrous perchlorate. In the fluoride experiments, the solutions were as above except that 25 ml. of water were replaced by sodium fluoride solution (20 g./l.). The ferrous solution was added from a burette in increments every 15 sec.

Products of Reaction.—(a) *αα-Dimethylbenzyl hydroperoxide.* In one experiment, 0·5 g. of peroxide in 500 ml. of 0·1N-sulphuric acid reacted with 20 ml. of ferrous sulphate solution (10 g. of $FeSO_4,7H_2O$ per l.) and 5 ml. of saturated potassium iodide solution. The reaction was complete within a few minutes. The iodine was removed with thiosulphate, and the mixture extracted with 30-ml. portions of carbon tetrachloride. This solution was concentrated by distillation, and the dried solution analysed by infra-red spectroscopy; 80% of the peroxide was recovered, of which 96% was in the form of 2-phenylpropan-2-ol and 4% acetophenone. In another experiment, 5. g. of hydroperoxide reacted with 10 ml. of the ferrous sulphate solution in 200 ml. of 0·1N-sulphuric acid. Saturated potassium iodide was added in 0·5-ml. increments at intervals of 15 min. The reaction required 2 hr. for completion. In this case 70% of the peroxide was recovered, all as the alcohol. No acetophenone could be detected.

(b) tert.-*Butyl hydroperoxide.* (Experiment with Dr. J. B. Williamson.) 4·5 G. of *tert.*-butyl hydroperoxide reacted with 50 ml. of 50% (w/w) potassium iodide in 500 ml. of 0·1N-sulphuric acid, 25 ml. of the ferrous sulphate solution being used as catalyst. After the addition of thiosulphate, the solution was distilled. 11 G. of distillate were extracted with ether. The extract was concentrated to one-quarter of its original volume by fractionation in a 5-plate column; material equivalent to 85% of the original hydroperoxide was recovered, all of which was found by infra-red analysis to be *tert.*-butyl alcohol (acetone not detected, *i.e.*, <0·5% of the hydroperoxide).

We thank the Directors of the Distillers Company Limited for permission to publish the work recorded in this and the preceding paper, and also Mr. A. R. Philpotts for the infra-red analyses.

The Distillers Company Limited, Research and Development Dept.,
Great Burgh, Epsom, Surrey. [*Received, June 26th*, 1952.]

446. *The Reaction between αα-Dimethylbenzyl Hydroperoxide and Ferrous Salts.*

By W. S. Wise and G. H. Twigg.

The reaction between ferrous ions and αα-dimethylbenzyl hydroperoxide has been studied in dilute acid aqueous solution in the absence of oxygen. Over a range of initial concentrations, 1·08 moles of ferrous ion are oxidised per mole of peroxide consumed; at high ferrous-ion concentrations, this ratio tends to 2. It is decreased by the presence of copper salts or methanol. The products of the reaction are acetophenone and 2-phenylpropan-2-ol. A mechanism is deduced from the experimental facts, and that for the reaction in the presence of oxygen is briefly considered.

The reaction between hydrogen peroxide and ferrous ions has been studied in some detail (Barb *et al.*, *Trans. Faraday Soc.*, 1951, **47**, 462, 591), but comparatively little is known about the reactions of organic hydroperoxides with ferrous salts. The reaction between αα-dimethylbenzyl hydroperoxide and ferrous ions was investigated in 1948 in these laboratories by Dr. J. B. Williamson; the main features then discovered are in general agreement with recently published work (Kharasch *et al.*, *J. Org. Chem.*, 1950, **15**, 763; Hawkins, *J.*, 1950, 2169; Fordham and Williams, *J. Amer. Chem. Soc.*, 1950, **72**, 4465; 1951, **73**, 1634; Kolthoff and Medalia, *ibid.*, 1949, **71**, 3789). The present work is mainly concerned with the reaction in dilute acidified aqueous solution in the absence of oxygen.

In the Absence of Oxygen.—(a) *Overall consumption ratios in dilute solution.* The consumption ratio, R, is the number of moles of ferrous ion oxidised per mole of peroxide consumed. No systematic investigation of the variation of R with the ratio of the initial concentration of reactants has been reported.

A simple method of analysis has been used. As is well known, the ferric ions produced liberate iodine quantitatively from iodide. The following paper shows that the iron salts present catalyse the reaction between iodide and the peroxide to form iodine. The total amount of iodine liberated from added iodide is thus a measure of the sum of the ferric-ion and peroxide concentrations. If the iodide is added after reaction between the ferrous ions and peroxide has ceased, then the value of R for the overall reaction can easily be calculated from the iodine titration.

Typical results are shown in Fig. 1, in which the total iodine liberated is plotted against the ratio of the initial concentrations of reactants at constant initial peroxide concentration. The full line, calculated for $R = 1{\cdot}08$, fits the experimental points over the whole of this range; *i.e.*, the value of R is constant and independent of the ratio of the initial concentrations over this range. The value of R appears to depend slightly on the acid concentration, as shown below:

	R	Ref.
0·01N-H_2SO_4	1·02	Williamson (personal communication)
0·1 ,,	1·08	Present work
1·0 ,,	1·12	Williamson (personal communication)
1·5 ,,	1·12, 1·15	Kolthoff and Medalia (*loc. cit.*)

The curve shown in Fig. 1 has been confirmed over a limited range ($[Fe^{2+}]_0/[RO_2H]_0 = 1$—3), the 2 : 2′-dipyridyl method (Jackson, *Ind. Eng. Chem. Anal.*, 1938, **10**, 302) being used to determine residual ferrous ion.

(b) *Overall consumption ratios with ferrous ions in great excess.* In these experiments, 25 ml. of the peroxide solution were added at a rate of 1 ml. every 30 sec. to a large excess of acidified ferrous sulphate solution, nitrogen being continuously bubbled through the mixture. The results obtained (Table 1) show that as the excess of ferrous ion over peroxide becomes large, the consumption ratio increases and tends to the limiting value of 2.

(c) *Variation in the consumption ratio throughout the reaction.* For conditions when the overall consumption ratio does not vary with the ratio of the initial concentrations, it is likely that $d[Fe^{2+}]/d[RO_2H]$ is constant throughout the reaction. An attempt was made

to confirm this by determining the variation of the concentration of each reactant with time. The reaction was stopped by rapidly extracting the peroxide with benzene, a method originally used by Kolthoff and Medalia. Difficulty was found, however, with

TABLE 1. *Consumption ratio when the ferrous ion is in great excess.*

$[Fe^{2+}]/RO_2H]$ *	275	1375	2750	5500
R	1·10	1·52	1·75	1·90

* The peroxide concentration is calculated as that of the 1-ml. increment.

their procedure. (i) A determination of the partition coefficient of the peroxide between benzene and water over a range of concentrations showed that under the conditions of their experiments about 30% of the peroxide would remain in the aqueous phase; it was therefore necessary to increase the ratio of the volume of benzene to that of the aqueous phase. (ii) At the low concentrations of peroxide which had to be used, the iodide method of peroxide analysis (Kokatnur and Jelling, *J. Amer. Chem. Soc.*, 1941, **63**, 1432) gave high results on the benzene extracts from actual runs, although made-up solutions of the

FIG. 1.

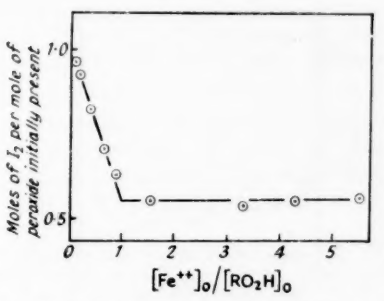

FIG. 2.

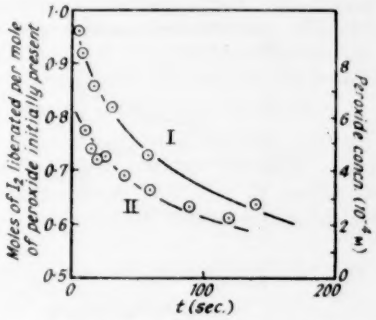

FIG. 1. *Graph of total iodine liberated against* $[Fe^{++}]_0/[RO_2H]_0$; $[RO_2H]_0$ *was* $1{\cdot}65 \times 10^{-3}$M. *The line drawn is the theoretical line* R = 1·08.

FIG. 2. *Curve I (left-hand scale): Graph of iodine liberated against time;* $[RO_2H]_0$ *was* $1{\cdot}65 \times 10^{-2}$M. *Curve II (right-hand scale): Graph of peroxide concentration against time. In both curves the line drawn is calculated from theory.*

peroxide in benzene gave exact results. The cause of this anomaly could not be found and a polarographic method of estimating the peroxide was developed. The results obtained for the peroxide analysis, shown in Fig. 2, are discussed later. (iii) The presence of organic substances in the aqueous phase caused the end-point of the titration of ferrous ions with ceric sulphate to drift. Also, at the beginning of reaction, the ferrous-ion determination was unsatisfactory owing to atmospheric oxidation. Reproducible results were difficult to obtain, and it was not possible to be certain that the consumption ratio did not tend to 2 initially. In order to settle this point a different procedure was used.

The iodide method used previously for measuring the overall consumption ratios was used. The reactants were mixed in a nitrogen atmosphere, and the iodide was added at a known time. If the value of R were 2, the total iodine liberated would be constant whatever the time of addition of iodide. Each mole of peroxide ($RO_2H \equiv I_2$) would produce 2 moles of ferric ions ($Fe^{3+} \equiv \frac{1}{2}I_2$). If, on the other hand, R is less than 2, the total iodine liberated will be less than that equivalent to the amount of peroxide originally present. The results of the experiments are shown in Fig. 2, from which it is clear that the total amount of iodine produced diminishes from the start of the reaction, so that R is less than 2 throughout the reaction.

(d) *Effect of added substances on the consumption ratio.* The effect of added methanol on the value of R is shown in Fig. 3, and it will be seen that comparatively large amounts decrease the value of R. At a given concentration of methanol, the value of R increases with increasing ferrous-ion concentration. Similar results were obtained on using ethanol

instead of methanol. The addition of 2-phenylpropan-2-ol to its limit of saturation in water did not affect the value of R in the absence of oxygen (in the presence of oxygen the value of R was increased slightly by the addition of the alcohol).

The value of the consumption ratio was apparently lower in the presence of added ferric salts, but this was traced to the presence of the copper impurity in the ferric salts used. Other impurities were cobalt and manganese, but these were found, in separate experiments, not to influence the value of the consumption ratio when added as manganous and cobaltous ions. " AnalaR " iron alum did not affect this ratio when added up to a ten-fold excess over the ferrous ion present, and separate experiments showed that addition of ammonium salts also did not affect it.

The variation in the value of R caused by the addition of copper ions is shown in Fig. 4. It is clear that in quite small amounts they cause an almost catalytic decomposition of the peroxide. The slope of the curve is so steep at low copper-ion concentrations that the point arises whether the consumption ratio of 1·08 found with ferrous salts alone is lower than the value 2 because of traces of copper salts in the reagents. This is considered to be unlikely because reproducible results are obtained with different batches of reagents.

FIG. 3.

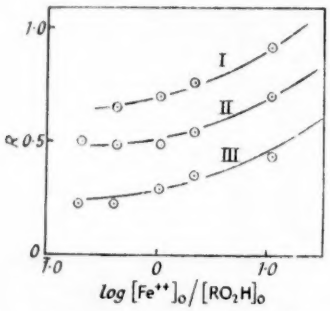

FIG. 4.

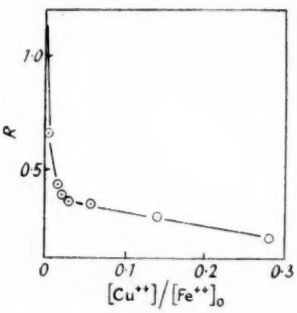

FIG. 3. *Variation of* R *with log* $[Fe^{++}]_0/[RO_2H]_0$ *at various methanol concentrations. These are, for curves I, II, and III respectively:* $[MeOH]/[RO_2H]_0 = 305, 770, 1540$. $[RO_2H]_0 = 1{\cdot}65 \times 10^{-3}$M.

FIG. 4. *Variation of* R *with* $[Cu^{++}]/[Fe^{++}]_0$; $[Fe^{++}]_0$ *was* $3{\cdot}6 \times 10^{-4}$M *and* $[RO_2H]_0$ $2{\cdot}0 \times 10^{-4}$M. *Iron analysis by* 2 : 2′*-dipyridyl method.*

Mechanism of the Reaction.—The initial reaction between ferrous ions and the hydroperoxide is the production of RO· radicals (R = $CPhMe_2$·):

$$Fe^{2+} + RO_2H \longrightarrow Fe^{3+} + RO\cdot + OH^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

These decompose to form acetophenone:

$$RO\cdot \longrightarrow C_6H_5\cdot CO\cdot CH_3 + CH_3\cdot \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The consumption ratio of about 1 would be explained if the methyl radical reacted further without decomposing either ferrous ions or the hydroperoxide. This simple view is wrong, however, for it will be shown below that the decomposition of the peroxide is faster than that given by the expression $k_1[Fe^{2+}][RO_2H]$, and also that the product of the hydroperoxide decomposition is not entirely acetophenone, but includes 2-phenylpropan-2-ol, which would be produced by the reaction:

$$Fe^{2+} + RO\cdot \longrightarrow Fe^{3+} + RO^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$H^+ + RO^- \longrightarrow ROH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (\text{fast}) \quad (3a)$$

A combination of reactions (1) and (3) would lead to the result that at high ferrous-ion concentrations the consumption ratio is 2, which is in fact the limiting value found in Table 1. It therefore seems that this reaction is significant at very high ferrous-ion concentrations. On the other hand, the fact that the consumption ratio is independent of the ratios of the initial concentrations of ferrous ion and peroxide over a wide range (as shown by Fig. 1) is taken to mean that reaction (3) is not significant under these conditions.

The constancy, at low ferrous concentrations, of the consumption ratio can only mean that the reaction which is in competition with reaction (2) for the RO· radical is one which does not involve ferrous ions or the peroxide, and we suggest

$$RO\cdot + H_2O \longrightarrow ROH + OH\cdot \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The OH· radical is removed by one of the following reactions :

$$OH\cdot + Fe^{2+} \longrightarrow OH^- + Fe^{3+} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4a)$$

$$OH\cdot + R\cdot O\cdot OH \longrightarrow H_2O + RO_2\cdot \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4b)$$

$$RO_2\cdot + Fe^{2+} \longrightarrow RO_2^- + Fe^{3+}$$

which are fast compared with reaction (4).

The fate of the methyl radical produced in reaction (2) must now be considered. The reaction $2CH_3\cdot \longrightarrow C_2H_6$ will be significant at high concentrations; ethane was found by Hawkins (*loc. cit.*) and Kharasch *et al.* (*J. Org. Chem.*, **1950**, **15**, 763). In the present experiments, it will not be significant, but Kharasch's finding (*loc. cit.*) of methanol as a major product indicates that the methyl radical reacts by

$$CH_3\cdot + RO\cdot OH \longrightarrow CH_3\cdot OH + RO\cdot \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

This type of reaction has been shown to take place in the thermal decomposition of αα-dimethylbenzyl hydroperoxide in cumene (Twigg, *Discuss. Faraday Soc.*, **1953**, **14**, 240). Kharasch, Arimoto, and Nudenberg (*J. Org. Chem.*, **1951**, **16**, 1556) have proposed, as an alternative to the reaction sequence represented by equations (2) and (5), the following :

$$CPhMe_2\cdot O\cdot + CPhMe_2\cdot O\cdot OH \longrightarrow C_6H_5\cdot CO\cdot CH_3 + CH_3\cdot OH + CPhMe_2\cdot O\cdot$$

There is no evidence in favour of this reaction; in particular, the reaction is absent in the thermal decomposition of αα-dimethylbenzyl hydroperoxide. Although equivalent chemically, it is different kinetically from reactions (2) and (5); it would imply a dependence of the consumption ratio on the peroxide concentration, which has not been found.

By combination of equations (1)—(5), and assumption of a stationary concentration for the radicals, the consumption ratio R is calculated to be :

$$R = \frac{d[Fe^{2+}]}{d[RO\cdot OH]} = \frac{2}{1 + k_2/(k_3[Fe^{2+}] + k_4[H_2O])}$$

At low ferrous-ion concentrations, this expression is independent of ferrous and peroxide concentrations, and at sufficiently high ferrous concentrations it tends to the value of 2, as found experimentally.

Similarly, the rate of disappearance of peroxide is

$$-d[RO\cdot OH]/dt = (2/R)k_1[Fe^{2+}][RO\cdot OH]$$

In Fig. 2 the lines drawn represent the course of the reactions calculated by using $R = 1{\cdot}08$, and $k_1 = 1{\cdot}07 \times 10^{10} \exp\{-12{,}000/RT\}$ l. mole^{-1} sec.$^{-1}$ as given by Fordham and Williams (*loc. cit.*, 1951).

The effect of added methanol can be explained by the additional reactions

$$CH_3\cdot OH + OH\cdot \longrightarrow H_2O + \cdot CH_2\cdot OH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

$$CH_3\cdot OH + RO\cdot \longrightarrow R\cdot OH + \cdot CH_2\cdot OH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

$$\cdot CH_2\cdot OH + Fe^{3+} \longrightarrow CH_2\cdot O\cdot + Fe^{2+} + H^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

These equations, together with those above, give an expression for the consumption ratio that is in agreement with the results shown in Fig. 3.

The catalysis by copper has not been investigated in any detail, but the facts that it does not take place in the absence of ferrous ions and that the production of acetophenone is increased suggest that the copper catalyses the decomposition of the RO· radical to acetophenone, possibly by

$$CPhMe_2\cdot O\cdot + Cu^{2+} \longrightarrow Ph\cdot CO\cdot CH_3 + CH_3^+ + Cu^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

followed by the rapid reactions

$$CH_3^+ + H_2O \longrightarrow CH_3\cdot OH + H^+$$

$$Cu^+ + Fe^{3+} \longrightarrow Cu^{2+} + Fe^{2+}$$

Products of the Reaction.—Some results have been reported by Kharasch *et al.* and also by Hawkins (*locc. cit.*), who used high concentrations of reactants. Some difficulty has been found in the present work in recovering the products from the reaction carried out under controlled conditions. When the ferrous solution is added to a high concentration of peroxide under conditions where the rate of mixing is limiting, the consumption ratio is less than 1 and the proportion of hydroperoxide recovered as acetophenone is at least about 70%.

It has not been possible to recover the products from dilute solutions when the consumption ratio is 1·08. By increasing the concentrations to about 0·02M and adding the hydroperoxide solution rapidly to the ferrous solution, a consumption ratio of 1·20 was obtained. The acetophenone found was 39% of the hydroperoxide taken and the alcohol 26%, with 35% of the hydroperoxide unrecovered. In another experiment, by using a chemical method of estimating acetophenone, 33 ± 10% of the peroxide was recovered as acetophenone. For the reaction scheme proposed above for dilute solutions, the amount of hydroperoxide recovered as acetophenone should be 46%. The agreement with the above results is within the experimental error. When the peroxide solution is added slowly to a large excess of ferrous solution, the amount of acetophenone recovered was about 10% of the hydroperoxide taken. This is evidently due to reaction (3) becoming significant.

Owing to the experimental difficulties, the analysis of the products does not provide conclusive evidence for the reaction scheme proposed above, but it shows that a considerable amount of 2-phenylpropan-2-ol is produced by the reaction between ferrous ions and hydroperoxide.

The Reaction in the Presence of Oxygen.—Although most of the present experimental work has been confined to the study of the reaction in the absence of oxygen, it is possible to suggest a tentative mechanism for these conditions. The salient feature is that in the presence of oxygen the consumption ratio increases as the ferrous-ion concentration increases, and can exceed the value of 6 (Kolthoff and Medalia, *loc. cit.*; Fordham and Williams, *loc. cit.*, 1950). The latter authors' explanation involves the decomposition of the RO· radical to acetophenone and a methyl radical, followed by the oxidation of the latter to formic acid. At most, seven ferrous ions would be oxidised per methyl radical during this process, and the number would be less through removal of HO_2· radicals by reaction with ferric ions (Barb *et al.*, *loc. cit.*). Thus, in order to account for the very high consumption ratios found, most of the peroxide would have to be converted into acetophenone. Experiments have been carried out in which peroxide solution was slowly dropped into a solution of acidified ferrous sulphate through which oxygen was vigorously bubbled. Of the original peroxide, 13% was found as acetophenone, 67% as phenylpropan-2-ol and 20% was not recovered, while the consumption ratio was 4.

A possible explanation may be based on the equilibria suggested by Weiss (*Nature*, 1934, **135**, 648), *viz.*,

$$Fe^{2+} + O_2 \rightleftharpoons Fe^{3+} + O_2^- \qquad H^+ + O_2^- \rightleftharpoons HO_2\cdot$$

It is well known that if ferric ions are removed as fluoride complex, ferrous ions are rapidly oxidised by molecular oxygen. In the present case, it seems possible that the HO_2· radicals might react with one of the species present, *e.g.*:

$$HO_2\cdot + RO_2H \longrightarrow H_2O_2 + RO_2\cdot \quad \ldots\ldots\ldots (10)$$

followed by

$$Fe^{2+} + RO_2\cdot \longrightarrow Fe^{3+} + RO_2^-$$
$$RO_2^- + H^+ \longrightarrow RO_2H$$
$$2Fe^{2+} + H_2O_2 \longrightarrow 2Fe^{3+} + 2OH^-$$

Reaction (10) is analogous to reaction (4*b*). A plausible explanation of the reaction in the presence of oxygen can therefore be made.

Experimental

Materials.—Water distilled in Pyrex glass from alkaline permanganate was used. Analytical-grade reagents were used except for the reagent-grade ferric sulphate [Section (d)], which contained as impurities: Co, 100; Cu, 2000; Mn, 3100; Pb, 650; Zn, 7·5 p.p.m. of the

salt. "AnalaR" iron alum contained 9 p.p.m. of Cu. These analyses were carried out by Mr. E. Archer. The αα-dimethylbenzyl hydroperoxide was prepared by oxidation of *iso*propylbenzene, and after extraction with light petroleum from the sodium salt was distilled in a molecular still before use. Its purity was 98% by the iodide method (Skellon and Wills, *Analyst*, 1948, **73**, 78).

Whenever appropriate, solutions and solvents were degassed by oxygen-free nitrogen before used. To obtain the results given in Fig. 1, 100 ml. of ferrous solution 0·1N in sulphuric acid were placed in a "Quickfit" B34 test-tube fitted with a wash-bottle head. 25 Ml. of 0·1% aqueous acidified hydroperoxide were then quickly added through a side-tube. When reaction had ceased, 5 ml. of potassium iodide solution (50% w/w) were added, and the liberated iodine was titrated with 0·05N-thiosulphate in a nitrogen atmosphere. The experiments on the variation in consumption ratio throughout the reaction were carried out similarly, except that the iodide was added at a known time after the reaction was started. Similar experiments were carried out for the other consumption ratio experiments. All experiments were carried out with the solution 0·1N in sulphuric acid.

The variation in the hydroperoxide concentration determined by the benzene-extraction method was carried out as follows. The reaction mixture was contained in a wide-necked flask kept in a thermostat at 25° and fitted with a stirrer. Side-arms were fitted through which nitrogen could be blown over the mixture and also benzene brought into the flask by applying nitrogen pressure to a separate vessel. A number of control experiments ensured that the rates of degassing and extraction were adequate. 100 Ml. of 0·1% hydroperoxide solution 0·1N in sulphuric acid were placed in the vessel and 5 ml. of ferrous sulphate solution were then added. At a noted time 100 ml. of benzene were blown into the vessel. After the contents of the vessel had been stirred vigorously for 5 sec., the two phases were separated. The ferrous-ion concentration in the aqueous phase was determined by titration with ceric sulphate. The benzene phase was evaporated in the presence of 25 ml. of 0·1N-sodium hydroxide (to retain the hydroperoxide as the sodium salt) by a stream of warm nitrogen. The solution was neutralised with acid and buffered by addition of solid potassium hydrogen phthalate. After being degassed with nitrogen, it was placed in a polarographic cell and the hydroperoxide estimated. αα-Dimethylbenzyl hydroperoxide has been found to give an irreversible wave with a maximum at −0·1 v (Godin and Wise, unpublished results).

In the experiments on the products, the solutions were mixed in a nitrogen atmosphere, and the products extracted with carbon tetrachloride. The resulting solution was concentrated, a 10-plate column being used to remove carbon tetrachloride, and the solutions were analysed by infra-red spectroscopy. No other products except acetophenone and the alcohol were found. In the chemical analyses the products were extracted into benzene, and the hydroxylamine method (Maltby and Primavesi, *Analyst*, 1949, **74**, 498) was used to determine acetophenone. The results of these experiments are summarised in Table 2.

TABLE 2. *Products of the reaction.*

$[RO_2H]$ initially, 10^{-3} mole	$[Fe^{2+}]$ initially, 10^{-3} mole	Initial vol., ml.	R	Hydroperoxide recovered as: COPhMe, %	$CPhMe_2$·OH, %	Unrecovered, %
5	10 [a]	500	0·8	71	7	22
16	90 [a]	500	0·8	61	6	33
16 [a]	90	500	1·2	39	26	35
3 [a]	106	200	—	5	43	52
2 [a]	100	200	—	11 [d]	—	—
2 [a]	10	200	—	28 [d]	—	—
2 [b]	5 [b]	200	1·1	33 [d]	—	—
2 [c]	100	500	4	13	67	20

[a] This reactant was added to the bulk of the other reactant. [b] Both dropped into 200 ml. of water at same rate. [c] In oxygen atmosphere. [d] Analysis by hydroxylamine method.

THE DISTILLERS COMPANY LIMITED, RESEARCH AND DEVELOPMENT DEPT.,
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447. *Triterpenoids. Part XIII.* Phyllanthol, the First Hexacarbocyclic Triterpenoid.*

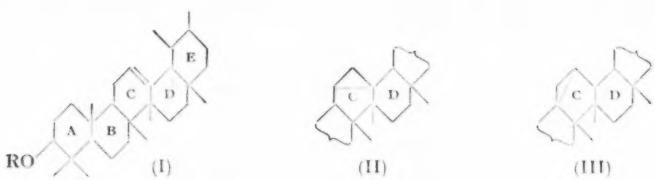
By D. H. R. Barton and P. de Mayo.

Phyllanthol (Alberman and Kipping, *J.*, 1951, 2296) has been characterised as a hexacarbocyclic secondary alcohol containing one *cyclo*propane ring. It is closely related to α-amyrin, for with acidic reagents the *cyclo*propane ring is opened to give the α-amyrin double bond. By the application of a new method for the location of *cyclo*propane rings it has been shown that phyllanthol is not 10 : 12- or 11 : 13-*cyclo*-α-amyranol. Some alternative possibilities are discussed.

The triterpenoid alcohol phyllanthol, $C_{30}H_{50}O$, was isolated by Alberman and Kipping (*J.*, 1951, 2296) from the root bark of *Phyllanthus engleri* (Pax.). Through the courtesy of Drs. Kipping and Alberman and the good offices of Sir John Simonsen, F.R.S., it has been possible to investigate it further.

Phyllanthol was characterised as a secondary alcohol by chromic acid oxidation to the corresponding ketone. The presence of a *cyclo*propane ring was established by the following evidence. (i) Phyllanthyl acetate gave only a weak colour with tetranitromethane, of an intensity comparable with that given by 3 : 5-*cyclo*cholestane. (ii) Phyllanthyl acetate was not attacked by hot perhydrol–acetic acid or by ozone. These are oxidation conditions to which even the very hindered double bond of α-amyrin acetate is susceptible (cf. McLean, Silverstone, and Spring, *J.*, 1951, 935, and references there cited). (iii) Phyllanthyl acetate showed no double-bond absorption in the far ultra-violet (cf. Bladon, Henbest, and Woods, *J.*, 1952, 2737; Halsall, *Chem. and Ind.*, 1951, 867). On these bases phyllanthol must have six, not five, rings; as such it is the first hexacarbocyclic triterpenoid. The only other known *cyclo*propane compounds of the triterpenoid series are *cyclo*artenone and its derivatives (Barton, *J.*, 1951, 1444; Bentley, Henry, Irvine, and Spring, *Chem. and Ind.*, 1953, 217).

Phyllanthol was shown to be closely related to α-amyrin by the following experiments. (*a*) Wolff–Kishner reduction of phyllanthone afforded phyllanthane which was smoothly converted into α-amyrene by refluxing hydrochloric–acetic acid. (*b*) Similar treatment of phyllanthyl acetate gave α-amyrin acetate in good yield, further identified by hydrolysis to α-amyrin and by conversion of the latter into α-amyrin benzoate. (*c*) Treatment of phyllanthyl acetate in chloroform with hydrogen chloride gas also furnished α-amyrin acetate.



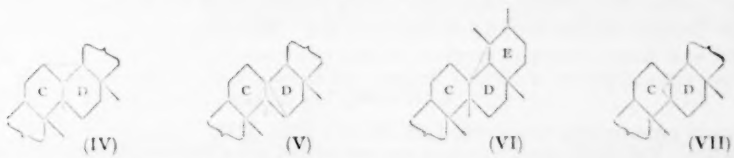
(I) (II) (III)

The simplest interpretation of these results is that phyllanthol is a *cyclo*propane derivative of α-amyranol with one apex of the *cyclo*propane ring terminating at $C_{(12)}$ or $C_{(13)}$. On the basis of the α-amyrin formula (I; R = H) (Meisels, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1949, **32**, 1075), there are then six possible representations for phyllanthol (II)—(VII). On biogenetic grounds (II) seemed to deserve prior consideration.

The precise location of a *cyclo*propane ring in an organic structure is not easily determined. However, if the *cyclo*propane ring were opened with deuterium chloride, the

* Part XII, *J.*, 1953, 1842.

position of the deuterium atom thus introduced would reveal one point of attachment of the ring. Our development of this new method for the location of *cyclo*propane rings was made possible by the generous co-operation of Dr. T. F. Gallagher and Dr. D. K. Fukushima (of the Sloan-Kettering Institute, New York) in the carrying out of precision deuterium micro-analyses (cf. Fukushima and Gallagher, *J. Biol. Chem.*, in the press).



(IV) (V) (VI) (VII)

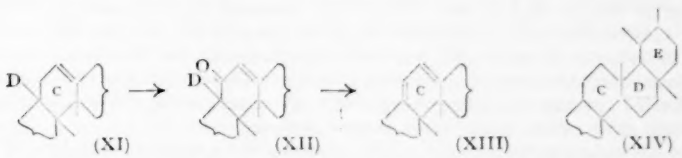
If phyllanthyl acetate had formula (II), treatment with deuterium chloride would give 11-deutero-α-amyrin acetate (VIII) which on chromic acid oxidation would afford the undeuterated 11-keto-α-amyrin acetate (IX). As expected, phyllanthyl acetate gave in this way a deuterated α-amyrin acetate having 2·65 atoms % excess of deuterium (theor. 1·9). Oxidation, however, afforded an 11-keto-α-amyrin acetate with the deuterium content (2·65 atom %) unchanged (theor. 2·0). Phyllanthol cannot, therefore, have formula (II).

(VIII) (IX)

The introduction of more than the theoretical amount of deuterium deserves brief comment. There are two reasonable explanations. (*a*) The acetate residue could have been deuterated through the ester enol. (*b*) The vinyl hydrogen at $C_{(12)}$ in α-amyrin acetate could be replaced by D^+ by the mechanism indicated * to give 12-deutero-α-amyrin acetate (X). That (*b*) was probably the correct explanation was demonstrated as follows. Alkaline hydrolysis of the deuterated (2·65 atom %) α-amyrin acetate followed by re-acetylation afforded a deuterated α-amyrin acetate with unchanged deuterium content.

(I) (X)

Another formula (III) for phyllanthol, which would appear reasonable on biogenetic grounds, has been excluded in the following way. On the basis of (III), deuteration of phyllanthyl acetate would afford 10-deutero-α-amyrin acetate (XI), which on oxidation would furnish 10-deutero-11-keto-α-amyrin acetate (XII) transformable by lithium



(XI) (XII) (XIII) (XIV)

aluminium hydride reduction followed by dehydration and re-acetylation into a deuterium-free α-amyra-10 : 12-dienyl acetate (XIII) (Spring *et al.*, *J.*, 1937, 249; 1938, 1233; 1939, 1075). A repetition of the treatment of phyllanthyl acetate with deuterium chloride

* This possibility was pointed out to us by Dr. D. K. Fukushima, to whom we express our best thanks.

gave a deuterated α-amyrin acetate (2·55 atom %), in agreement with the first experiment. Conversion into the acetate (XIII) afforded a compound in which all the deuterium had been retained. We have not so far been able to pursue our investigations further owing to the difficulty of obtaining additional supplies of phyllanthol.

Further discussion of the other possible formulæ is not justified at present. We point out, however, that there remain for consideration formulæ such as (XIV) * which represent simple modifications of the ordinary α-amyrin carbon skeleton.

Experimental

For general experimental details see Part VII (*J.*, 1952, 2339). $[\alpha]_D$ are in $CHCl_3$.

Phyllanthol.—The crude alcohol (7·5 g.) was acetylated and chromatographed over alumina. Elution with benzene and crystallisation from chloroform–methanol afforded phyllanthyl acetate (2·5 g.), m. p. 262—264°, $[\alpha]_D$ +48° (*c*, 1·02), in good agreement with the constants recorded by Alberman and Kipping (*loc. cit.*). Phyllanthyl acetate was recovered unchanged (m. p. and mixed m. p.) after (*a*) treatment in acetic acid with perhydrol on the steam-bath for 1 hr., (*b*) treatment in chloroform with ozone for 30 min. at room temperature. It showed no significant absorption in the ultra-violet between 200 and 225 mμ.

Alkaline hydrolysis of the acetate gave phyllanthol, m. p. 227—228° (from chloroform–methanol), $[\alpha]_D$ +45° (*c*, 1·60) (Found: C, 84·0; H, 11·7. Calc. for $C_{30}H_{50}O$: C, 84·4; H, 11·8%).

Phyllanthone.—Phyllanthol (170 mg.) in acetic acid (15 ml.) and " AnalaR " benzene (3 ml.) was treated with chromium trioxide (40 mg.) in the minimum of water, during 20 hr. at room temperature. The product was crystallised from methanol, to give *phyllanthone*, m. p. 164—165°, $[\alpha]_D$ +52° (*c*, 1·52) (Found: 83·3; H, 11·1. $C_{30}H_{48}O,\frac{1}{2}CH_3{\cdot}OH$ requires C, 83·2; H, 11·4%).

Phyllanthane.—The above-mentioned ketone (100 mg.) in ethanol (2·5 ml.) containing dissolved sodium (150 mg.) and 100% hydrazine hydrate (1 ml.) was heated in a sealed tube at 205° overnight. The product was chromatographed over alumina; elution with light petroleum and crystallisation from chloroform–methanol furnished phyllanthane, m. p. 166—167° (mixed m. p. with phyllanthone, 140—150°), $[\alpha]_D$ +46° (*c*, 1·65) (Found: C, 88·0; H, 12·25. $C_{30}H_{50}$ requires C, 87·75; H, 12·25%).

Phyllanthane (20 mg.) in acetic acid (5 ml.) containing concentrated hydrochloric acid (0·5 ml.) was refluxed for 45 min. The product, on crystallisation form chloroform–methanol, was identified as α-amyrene by m. p., mixed m. p., and rotation {$[\alpha]_D$ +87° (*c*, 0·55)}.

Isomerisation of Phyllanthyl Acetate.—(i) The acetate (50 mg.) in chloroform (12 ml.) was treated with a stream of hydrogen chloride for 4 hr. After removal of the chloroform *in vacuo*, the product was crystallised from chloroform–methanol, to give α-amyrin acetate (20 mg.), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +73° (*c*, 1·58)}. The identity was confirmed by hydrolysis to α-amyrin, m. p. and mixed m. p. 180—183°, $[\alpha]_D$ +84° (*c*, 1·85), benzoylation of which afforded α-amyrin benzoate, m. p. and mixed m. p. 192—193°, $[\alpha]_D$ +91° (*c*, 1·61).

(ii) The acetate (50 mg.) in acetic acid (10 ml.) and concentrated hydrochloric acid (1·5 ml.) was refluxed for 30 min. The product, crystallised from chloroform–methanol, gave α-amyrin acetate (35 mg.), identified by m. p. and mixed m. p.

(iii) The acetate (150 mg.) in dry alcohol-free chloroform (5 ml.) and two drops of 99·65% deuterium oxide (Norsk Hydro) was stirred by a magnetic stirrer, and the containing flask evacuated. Gaseous deuterium chloride (prepared by addition of distilled phosphorus trichloride to 99·65% deuterium oxide) was then admitted, and the flask was re-evacuated and then filled once more with gaseous deuterium chloride. The system was then sealed and, after a further 15 min.' stirring, was left overnight at room temperature. Working up as described under (i) above gave *x*-deutero-α-amyrin acetate (115 mg.).

x-*Deutero*-11-*keto*-α-*amyrin Acetate.*—The deuterated α-amyrin acetate (55·2 mg.) in " AnalaR " acetic acid (4 ml.) was treated with chromium trioxide (28 mg.) in " AnalaR " acetic acid (1 ml.) at 85° during ¾ hr. After the addition heating was continued for ½ hr. at the end of which some of the chromium trioxide remained unconsumed. Crystallisation from chloroform–methanol gave *x*-deutero-11-keto-α-amyrin acetate (26 mg.), m. p. 270—272°.

* This was first suggested to us by Professor R. B. Woodward (Harvard) to whom we express our best thanks.

x-*Deutero*-α-*amyra*-10 : 12-*dienyl Acetate*.—*x*-Deutero-11-keto-α-amyrin acetate (300 mg.) in dry ether (80 ml.) and lithium aluminium hydride (300 mg.) in the same solvent (10 ml.) were refluxed for 30 min. After isolation the crude product was refluxed for 20 min. in acetic anhydride (11 ml.) containing toluene-*p*-sulphonic acid (20 mg.). Crystallisation from methanol gave *x*-deutero-α-amyra-10 : 12-dienyl acetate, m. p. 166—167°, $[\alpha]_D$ +335° (*c*, 2·15).

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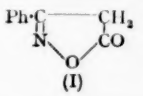
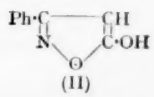
NOTES.

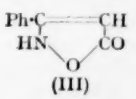
448. 3-*Phenylisooxazol-5-one*.

By C. L. ANGYAL and R. J. W. LE FÈVRE.

WHEN (*J.*, 1949, 2812) the dipole moment of "3-phenyl*iso*oxazol-5-one" was reported as 4·9 D, it was realised that the chemical evidence cited in Beilstein's "Handbuch" (XXVII, 200; XVII, 1st Ergänzungsband, 278) suggested a possible tautomerism of (I) to (II)—or perhaps (III). The present note records some new experiments designed to investigate these possibilities.


(I)


(II)


(III)

"Bromine titration," gave results corresponding to enol percentages of *ca.* 190, in other words the over-all reaction involved roughly twice the amount of bromine needed if (I) were 100% enolised. Further, the "4 : 4-dibromo-3-phenyl*iso*oxazol-5-one" described by A. Meyer (*Ann. Chim. Phys.*, 1914, **9**, 135, 252; *Compt. rend.*, 1913, **154**, 1511), although liberating 1 mol. of iodine from sodium iodide in neutral aqueous-alcoholic solution, released two in media acidified with hydrochloric acid. It was evident therefore that the conventional bromine addition technique applied to the parent phenyl*iso*oxazolone might be complicated by a multiplicity of reactions and could not provide with certainty the information desired.

Dipole moments were next determined of substances related in structure to (I) and (II), *viz.*, of 4 : 4-dimethyl-3-phenyl*iso*oxazol-5-one (Haller and Bauer, *Compt. rend.*, 1911, **152**, 553, 1146; *Ann. Chim. Phys.*, 1924, **10**, 278), 5-methoxy-3-phenyl*iso*oxazole (Oliveri-Mandala and Coppola, *Atti R. Accad. Lincei*, 1911, **20**, 248), and Meyer's dibromo-derivative (*loc. cit.*), the values being 5·0, 3·8, and 4·5 D, respectively. Unfortunately, these figures, even when the obvious implications are considered of the moments now measured of ethyl *iso*propyl and ethyl *iso*propenyl ethers (1·4 D and $1{\cdot}4_5$ D) and that (3·07 D) recorded by Tappi and Springer (*Gazzetta*, 1940, **70**, 190) for 3-phenyl*iso*oxazole, do not settle the question because it is impossible to show convincingly from them that the moment of structure (II) would be markedly different from that of structure (I). Accordingly evidence has been sought from infra-red spectroscopy, Nujol mulls of each substance being examined as a preliminary; the Figure shows the detail emerging between 1000 and 1800 cm.$^{-1}$, and Table 1 lists the maxima. The first two substances have high absorption at positions approaching those recorded (Randall, Fowler, Fuson, and Dangl, "Infra-red Determination of Organic Structures," van Nostrand, 1949) for carbonyl in oil suspensions of compounds such as 3-methyl-1-phenylpyrazol-5-one (1812 cm.$^{-1}$) and

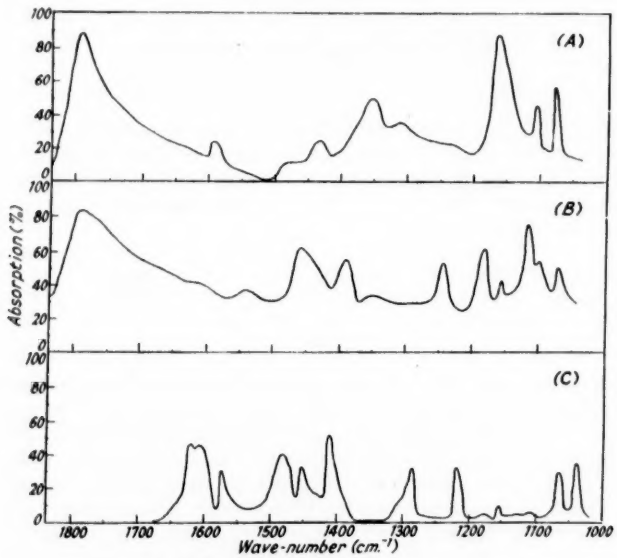
4-benzyl-2-phenyloxazol-5-one (1818 cm.$^{-1}$), and exceeding by 20—30 cm.$^{-1}$ those (1760—1770 cm.$^{-1}$) noted previously in the sydnones (Earl, Le Fèvre, Pulford, and Walsh, *J.*, 1951,

TABLE 1. *Absorption maxima* (*cm.*$^{-1}$).

"3-Phenyl*iso*oxazol-5-one"	—	1078	—	1105	1162	—	*ca.* (1240)	1309	1350
Dimethyl derivative	—	1070	1097	1115	1155	1182	1244	—	1350
Methoxy derivative	1038	1066	—	(1107)	1155	(1175)	1218	1283	—
"3-Phenyl*iso*oxazol-5-one"	—	1432	—	1486	—	1592	—	—	1792
Dimethyl derivative	1390	—	1459	—	1540	—	—	—	1788
Methoxy derivative	—	1412	1452	1482	—	1572	1602	1620	—

(Very weak absorptions shown by parentheses.)

2207). The absence of this feature in the third substance confirms that it is the *O*- and not the *N*-ether [*i.e.*, that it is derived from (II) and not from (III)]. Presumably bands due to the C=N linkage overlap those due to C=O and cause the broad absorption



(*A*) "3-Phenyl*iso*oxazol-5-one."
(*B*) 4 : 4-Dimethyl-3-phenyl*iso*oxazol-5-one.
(*C*) 5-Methoxy-3-phenyl*iso*oxazole.

seen between 1800 and 1650 cm.$^{-1}$. Most of the remaining peaks can be attributed to C–H linkages, the phenyl group, etc.

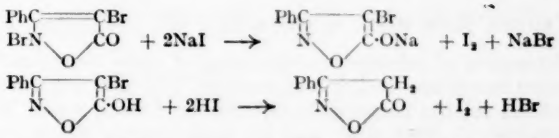
In the shorter-wave region, because Nujol has a broad absorption band at 2900—3000 cm.$^{-1}$, the spectrum of the parent compound was also run as a tetrachloroethylene mull and bands corresponding to phenyl (3075 cm.$^{-1}$) and methylene groups (2940 and 2985 cm.$^{-1}$) were identified. None of the substances showed signs of O–H or N–H bonds in the neighbourhood of 3 μ. A rejection of formulæ (II) and (III), while consistent with such lack of evidence, may not be safely concluded from it since the present observations were made on the crystalline solids—a state in which hydrogen bonding is often strongly developed among authentic hydroxyl-containing compounds, leading to a lowering of their O–H stretching frequencies from 3600 towards 3000 cm.$^{-1}$ and, in consequence, difficulty in distinguishing these from those due to C–H (compare, *e.g.*, various hydroxypyrimidines; Brownlie, *J.*, 1950, 3062; Short and Thompson, *J.*, 1952, 168).

Accordingly we sought to investigate the parent *iso*oxazolone around 3 μ as a solute.

Benzene—the solvent in which our dipole moment determinations (*J.*, 1949, 2812) had been made—was used (saturated solution). Between 2800 and 3800 cm.$^{-1}$ the spectrum of this solution was identical with that of benzene alone.

Again, no evidence of O–H could be seen. On the whole, therefore, we conclude that " 3-phenyl*iso*oxazol-5-one " is adequately represented by (I).

Finally we mention that the moment found for the dibromo-derivative of (I) would be equally explicable whether the two halogen atoms were both on $C_{(4)}$ of (I) or one each on $N_{(2)}$ and $C_{(4)}$ of (III)—this follows from elementary vectorial considerations since μ_{N-Br} is *ca.* zero (Theilacker and Fauser, *Annalen*, 1939, **539**, 103); however, the " bromine titration " observations already noted are more easily understood by a formula based on (III). The fact that the dibromo-derivative liberates iodine equivalent to one bromine atom from a neutral solution is a strong indication that one of the bromine atoms is attached to nitrogen. After the end-point is reached, the solution can be acidified and another mole of iodine liberated. At the same time a precipitate is formed which can be isolated and identified as the parent compound. The following equations are suggested for these reactions :



Experimental.—Substances. These were prepared by methods recorded in the literature, as follow : 3-phenyl*iso*oxazol-5-one, m. p. 151—152° (from alcohol), from ethyl benzoylacetate and hydroxylamine (Hantzsch, *Ber.*, 1891, **24**, 502); 5-methoxy-3-phenyl*iso*oxazole, m. p. 77—77·5° (from aqueous alcohol), from diazomethane and the preceding compound (Oliveri-Mandala and Coppola, *Atti R. Accad. Lincei*, 1911, **20**, I, 248); 4 : 4-dibromo-3-phenyl*iso*oxazol-5-one, m. p. 74—75° (from aqueous alcohol), from the parent by bromination in acetic acid (Meyer, *Ann. Chim. Phys.*, 1914, **9**, 135, 252); 4 : 4-dimethyl-3-phenyl*iso*oxazol-5-one, m. p. 69—70° (from aqueous alcohol), from ethyl dimethylbenzoylacetate and hydroxylamine (Haller and Bauer, *Compt. rend.*, 1911, **152**, 553, 1146; *Ann. Chim. Phys.*, 1924, **10**, 278); ethyl *iso*propenyl ether, b. p. 57—61°, from acetone diethyl acetal by treatment with phosphoric oxide in quinoline (Claisen, *Ber.*, 1898, **31**, 1019).

Dipole moment determinations. These have been made by customary methods (cf. *J.*, 1948, 1949; 1949, 333). Essential data are given in Tables 2 and 3 under headings explained in

TABLE 2. *Dielectric constant and density measurements.*

	5-Methoxy-3-phenylisooxazole				*4 : 4-Dimethyl-3-phenylisooxazol-5-one*		
10^5w_2	0	533	1068	1638	245	436·4	563·2
ε_{25}	2·2725	2·3205	2·3706	2·4247	2·3059	2·3335	2·3578
d_4^{25}	0·87378	0·87502	0·87634	0·87773	0·87435	0·87476	0·87515

	4 : 4-Dibromo-3-phenylisooxazol-5-one				*Ethyl isopropyl ether*				
10^5w_2	0	674	844	1235	1182·4	1680·6	2043·7	2531·5	2795·6
ε_{30}	2·2628	2·3090	2·3201	2·3476	2·2866	2·2982	2·3044	2·3149	2·3203
d_4^{30}	0·86718	0·86998	0·87126	0·87284	0·86524	0·86433	0·86377	0·86297	0·86258

	Ethyl isopropenyl ether						
10^5w_2	979·8	1431·2	2352·7	2861·2	3675·7	3809·8	4108·6
ε_{30}	2·2870	2·2966	2·3200	2·3305	2·3537	2·3556	2·3642
d_4^{30}	0·86607	0·86549	0·86428	0·86386	0·86284	0·86281	0·86253

TABLE 3. *Calculation of results.*

Solute	M_2	Mean $\alpha\varepsilon_1$	Mean β	$_\infty P_2$	R_2	μ (D)
5-Methoxy-3-phenyl*iso*oxazole	175·2	9·16	0·272	345	45 *	$3·8_2$
4 : 4-Dimethyl-3-phenyl*iso*oxazol-5-one	189·2	14·0	$0·262_5$	546	50 *	$4·9_3$
4 : 4-Dibromo-3-phenyl*iso*oxazol-5-one	318·8	6·84	0·525	467	56 *	$4·4_4$
Ethyl *iso*propyl ether	88·1	2·05	−0·192	70·3	31·5 †	$1·3_9$
Ethyl *iso*propenyl ether	86·1	2·43	$-0·134_5$	73·2	31 ‡	$1·4_5$

* Calc. from R_2 = 40·5 c.c. for phenyl*iso*oxazolone (*J.*, 1949, 2812).
† Mean between values for Et_2O and Pr^i_2O (cf. *J.*, 1952, 1643).
‡ Previous R_2 minus $2R_H$, plus $R_{\text{double bond}}$.

Trans. Faraday Soc., 1950, **46**, 1, except that subscripts 1 and 2 here refer respectively to the solvent and solute (this is the reverse of the convention formerly adopted; cf. *J.*, 1952, 1932).

Infra-red spectra. These were taken on a Perkin-Elmer spectrometer model 12-C, calibration being effected by means of the curves shown by Oetjen, Kao, and Randall (*Rev. Sci. Instr.*, 1942, **13**, 515) for ammonia gas or atmospheric carbon dioxide and water vapour.

The authors acknowledge with gratitude the help of Mr. R. L. Werner with the infra-red spectra.

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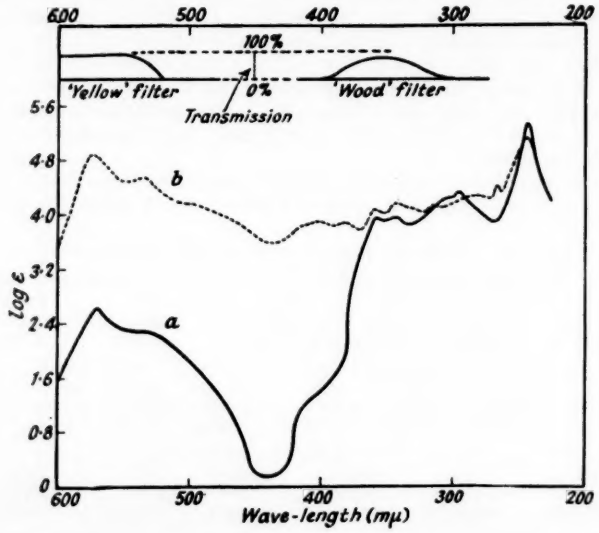
449. *Reversible Appearance and Disappearance of Coloured Modifications of Some Compounds as a Result of Irradiation at Low Temperatures.*

By YEHUDA HIRSHBERG, EPHRAIM H. FREI, and ERNST FISCHER.

THE reversible formation of coloured modifications of some compounds in solution, as a result of ultra-violet irradiation at low temperatures, was first described by Hirshberg for dianthronylidene and related compounds (Hirshberg, *Compt. rend.*, 1950, **231**, 903; cf. Hirshberg and Fischer, *J.*, 1953, 629), and for some spirans (Fischer and Hirshberg, *J.*, 1952, 4522). In these experiments the rate of the spontaneous reversion of the coloured

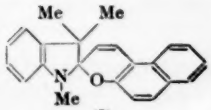
Absorption spectrum of (I) *at* 173° K (a) *before and* (b) *after ultra-violet irradiation.*



to the colourless modifications was measured at a series of temperatures, and Arrhenius parameters of the reversion reaction were estimated. We have now found that the reversion to the colourless form can also be brought about by irradiation with light corresponding to the absorption maximum of the coloured modification in the visible region.

Experimental.—When a solution of 1 : 3 : 3-trimethylindoline-2-*spiro*-6′-(2′ : 3′-β-naphthopyran) (I) in an ethanol–methanol mixture at 173° K is irradiated with light in the 365-mμ region (from a mercury arc and a Wood's filter; transmission about 66% of the 365-mμ group and 10% of the 313-mμ group), an intense mauve colour is produced (Figure). At this temper-

ature both the coloured and the colourless modification are stable. (Extrapolation of the kinetic data to 173° K gives a half-life time of about 6 weeks for the spontaneous decay of colour at this temperature.)



(I)

Irradiation of the coloured solution with light from a 300-w incandescent lamp passed through a " yellow " filter (transmission 80—90% between 800 and 540 mμ and none below 500 mμ) results in a steady decrease in intensity of colour. The cycle of colour formation by ultra-violet irradiation and its eradication by " yellow " irradiation can be repeated many times.

Similar observations were made on solutions of (I) in non-polar solvents.

Work is now in progress on other compounds showing indications of similar behaviour.

We acknowledge our indebtedness to Dr. Gabriel Stein, who suggested the irradiation in the visible region independently of one of us (E. H. F.).

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[*Received, February 19th,* 1953.]

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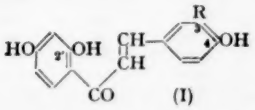
450. *The Isolation of 2′ : 4 : 4′-Trihydroxychalkone from Yellow Varieties of* Dahlia variabilis.

By E. C. BATE-SMITH and T. SWAIN.

PRICE (*J.*, 1939, 1017) isolated the chalkone butein (I; R = OH) from selected genotypes of yellow varieties of *Dahlia variabilis* and concluded that this compound was primarily responsible for the colour in all yellow dahlias. In 1949 one of us (E. C. B.-S.) noted that both unhydrolysed and hydrolysed extracts of petals of yellow dahlias, when separated on paper chromatograms in butanol–acetic acid–water (4 : 1 : 5), showed the presence, in addition to butein (R_F 0·78), of a faster-running aglycone (R_F 0·87) which gave an orange colour with caustic alkali. On the basis of its R_M value (Bate-Smith and Westall, *Biochem. Biophys. Acta*, 1950, **4**, 427) and the interrelations of the other flavonoid compounds in *Dahlia variabilis* (Lawrence and Scott-Moncrieff, *J. Genetics*, 1935, **30**, 155) it was presumed to be 2′ : 4 : 4′-trihydroxychalkone (I; R = H).



(I)

In the present work this constituent was separated from butein in the hydrolysed extracts of the yellow dahlia " Pius IX " on columns of " Magnesol " (cf. Ice and Wender, *Arch. Biochem. Biophys.*, 1952, **38**, 185). The compound and its triacetate did not depress the melting points of synthetic 2′ : 4 : 4′-trihydroxychalkone and its triacetate respectively (Nadkarni and Wheeler, *J.*, 1938, 1320). Degradation on a micro-scale of both the natural and the synthetic chalkones with potassium hydroxide and examination of the products by paper chromatography (Lindstedt and Misiorny, *Acta Chem. Scand.*, 1951, **5**, 1) gave resacetophenone and *p*-hydroxybenzoic acid. The compound from " Pius IX " had similar R_F values to synthetic (I; R = H) on paper chromatograms in several solvent systems (Table 1). Further the spectra of the compound in ethanolic M/500-sodium ethoxide (Mansfield, Swain, and Nordström, *Nature*, in the press) and 0·17% alcoholic

aluminium chloride solution (cf. Gage and Wender, *Proc. Oklahoma Acad. Sci.*, 1949, **30**, 145; *Chem. Abs.*, 1952, **46**, 3463*a*), and of the acetate in ethanol and 0·17% aluminium chloride solution were indistinguishable from those of the synthetic chalkone (I; R = H) and its acetate respectively in the same solvents (Table 2).

TABLE 1. R_F *Values and colour reactions of the chalkones, their acetates, and degradation products.*

		R_F in					
			BuOH–H_2O		EtOAc–H_2O		
No.		BuOH–AcOH–H_2O	plain paper	borate paper	plain paper	borate paper	$COMe_2$–H_2O 1 : 3 *
1	Natural chalkone	0·87	0·86	0·83	0·93	0·93	0·08
2	2′ : 4 : 4′-Trihydroxychalkone	0·87	0·86	0·83	0·93	0·93	0·08
3	Butein	0·78	0·80	0·02	0·87	0·03	0·03
4	Natural chalkone acetate	0·91	0·88	—	—	—	0·95
5	2′ : 4 : 4′-Trihydroxychalkone triacetate	0·91	0·88	—	—	—	0·95
6	Degradation product from natural chalkone	—	0·75 0·89	0·10 0·86	—	—	—
7	Degradation product from 2′ : 4 : 4′-trihydroxychalkone	—	0·73 0·88	0·11 0·86	—	—	—
8	*p*-Hydroxybenzoic acid	—	0·74	0·12	—	—	—
9	Resacetophenone	—	0·89	0·86	—	—	—

	Colour reactions				
		Fluorescence in :			
No.	$FeCl_3$ soln.	u.-v. light	u.-v. light + NH_3 vapour	NaOH	Diazotised † *p*-nitroaniline + Na_2CO_3
1	Brown	Brown	Golden yellow	Deep yellow	—
2	Brown	Brown	Golden yellow	Deep yellow	—
3	Green-brown	Orange	Reddish-orange	Orange	—
4	—	Dull violet	Faint yellow	Yellow	—
5	—	Dull violet	Faint yellow	Yellow	—
6	— —	— Green	— Brown	— —	Red Brown
7	— —	— Green	— Brown	— —	Red Brown
8	—	—	—	—	Red
9	—	Green	Brown	—	Brown

* Somewhat variable results. † Swain (*loc. cit.*).

TABLE 2. $\lambda_{max.}$ (mμ) *of the chalkones and their acetates in various solvents.*

	Ethanol		M/500-NaOEt		0·17% $AlCl_3$–EtOH	
Compound	Band I	Band II	Band I	Band II	Band I	Band II
Natural chalkone	370	240	440 *	245 *	422 *	236 *
2′ : 4 : 4′-Trihydroxychalkone	370	242	440 *	252 *	422 *	236 *
Butein	382	262	447	281	445	(324) †
Neutral chalkone acetate	312	—	—	—	312	—
2′ : 4 : 4′ Trihydroxychalkone acetate	312	—	—	—	312	—

* These spectra have a number of small inflections.
† This peak appears to be related to an inflection at 318 mμ in EtOH.

2′ : 4 : 4′-Trihydroxychalkone has not previously been isolated from natural sources. Its occurrence with butein is interesting since flavones and anthocyanins are linked biosynthetically (Lawrence and Scott-Moncrieff, *loc. cit.*) and gives further weight to the view that these compounds are formed from a common precursor (Robinson, *Nature*, 1936, **137**, 172).

Experimental.—Isolation of 2′ : 4 : 4′-trihydroxychalkone from "Pius IX." The white tips were removed from the ray florets and the remainder (112 g.) covered with alcohol (400 ml.) and disintegrated in a Waring blender, the pulp was re-extracted with alcohol (2 × 200 ml.), and

the combined extract taken to dryness *in vacuo*, yielding a dark orange, sticky solid (5·3 g.). [Attempts to free this from sugars on IRC-50 carboxylic acid ion-exchange resin (Gage *et al.*, *Science*, 1951, **113**, 422) were abandoned since the adsorptive capacity of the resin for the chalkones was too small.] The solid was hydrolysed with hydrochloric acid in 50% ethanol (100 ml.), diluted, neutralised to pH 4 (NaOH), and extracted with ethyl acetate. Removal of the solvent gave a dark brown sticky solid (1·26 g.) which showed the presence of butein, 2′ : 2 : 4′-trihydroxychalkone, and traces of glycosidic material as well as of free sugars (mainly glucose) on a paper chromatogram. The solid was dissolved in dry acetone, absorbed on acid-washed " Magnesol " (a synthetic magnesium silicate, Westvaco Chemical Division, South Charleston, W. Va.), and eluted with acetone, giving a fraction (0·65 g.) consisting of chalkones and a little sugar. This was applied to a column of unwashed " Magnesol–Celite 545 " (4 : 1) and developed with dry acetone, giving a fast running band of crude 2′ : 4 : 4′-trihydroxychalkone, and sugars only (0·31 g.). Recrystallisation from water and then dilute alcohol gave yellow crystals, m. p. 199·5—200·5° (Found : C, 65·3, 65·6, 66·0; H, 5·0, 5·1, 5·6. Calc. for $C_{15}H_{12}O_4.H_2O$: C, 65·7; H, 5·1%) (Nadkarni and Wheeler, *loc. cit.*, state that 2′ : 4 : 4′-trihydroxychalkone forms a monohydrate, m. p. 202—204°). The acetate separated from alcohol as colourless needles, m. p. 119·5—120° (Found : C, 65·6; H, 4·8. Calc. for $C_{21}H_{18}O_7$: C, 65·9; H, 4·7%).

Synthetic 2′ : 4 : 4′-trihydroxychalkone. The procedure described by Nadkarni and Wheeler (*loc. cit.*) gave an impure product. The method was improved by neutralisation to pH 8 only, extraction with ethyl acetate, and washing with saturated sodium sulphite solution and water. Removal of the solvent and extraction of the solid with benzene left almost pure chalkone. It recrystallised from aqueous alcohol as light orange-yellow rhombs, m. p. 202—203° alone or mixed with the natural product (Found : C, 65·9; H, 5·1%). The acetate had m. p. 120—120·5° alone or mixed with the acetate of the natural product (Found : C, 65·8; H, 4·9%).

Paper chromatography. The chromatograms were run as described by Swain (*Biochem. J.*, 1953, **53**, 200) but without strict temperature control. The results are shown in Table 1.

Micro-degradation. The chalkone (*ca.* 0·5 mg.) and a few drops of water and potassium hydroxide (*ca.* 0·1 g.) were heated until the initial dark orange colour disappeared (1—2 min.), diluted with water, acidified, and extracted with ether (0·5 ml.). It was run on paper chromatograms and the results are shown in Table 1.

Spectra. The spectra in ethanolic 0·002M-sodium ethoxide were plotted as described by Mansfield *et al.* (*loc. cit.*). The spectra in 0·17% alcoholic aluminium chloride were plotted after dilution of the original ethanolic solution (2·5 ml.) with 1% alcoholic aluminium chloride solution (0·5 ml.).

We thank the Westvaco Chemical Division, W. Va., U.S.A., for a gift of Magnesol. This paper forms part of the programme of the Food Investigation Board of the Department of Scientific and Industrial Research.

LOW TEMPERATURE RESEARCH STATION, CAMBRIDGE. [*Received, March 3rd*, 1953.]

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451. *The Acid-catalysed Hydrolysis of Benzoyl Fluoride.*

By C. W. L. BEVAN and R. F. HUDSON.

THE hydrolysis of benzoyl chlorides has been studied extensively and in no case has acid catalysis of these reactions been demonstrated (Olivier and Berger, *Rec. Trav. chim.*, 1927, **46**, 609; Hudson *et al.*, *J.*, 1950, 1729, 3529). Recently, it has been shown that in the hydrolysis of benzyl fluorides (Bernstein and Miller, *J. Amer. Chem. Soc.*, 1948, **70**, 3602) and of aliphatic fluorides (Chapman and Levy, *J.*, 1952, 1675) there is in many cases considerable acid catalysis. It therefore appeared of interest to examine the corresponding reactions of benzoyl fluoride.

The hydrolyses were carried out in aqueous acetone and a summary of the results is given in Table 1. Values of the pseudo-unimolecular constant k_1 were obtained by using 0·05N-hydrochloric acid in each case, and the catalytic hydrolysis constant, k_H, was calculated from the assumed relation, $k_1 = k_0 + k_H[HCl]$.

The rate constants k_0 and k_1 were calculated from the general expression for a first-order process, and in no case were significant deviations observed (cf. Table 2).

TABLE 1. *Solvolytic and catalytic rate constants at* 30°.

Concn. of H_2O vol. %	Concn. of H_2O moles/l.	$100k_0$, min.$^{-1}$	$100k_1$, min.$^{-1}$	$100k_H$, l. mole^{-1} min.$^{-1}$	Concn. of H_2O vol. %	Concn. of H_2O moles/l.	$100k_0$, min.$^{-1}$	$100k_1$, min.$^{-1}$	$100k_H$, l. mole^{-1} min.$^{-1}$
9·1	5·06	0·0034	0·0273	0·475	40·0	22·2	0·218	0·288	1·4
15·0	8·33	0·0136	0·0241	0·57	50·0	27·8	0·475	—	—
30·0	16·7	0·0928	—	—	70·0	38·9	2·18	2·33	3
37·5	20·83	0·170	—	—					

TABLE 2. *Determination of rate constants* (k_0, *in min.*$^{-1}$).

Benzoyl fluoride in 50% aqueous acetone at 30·0°; [C_6H_5·COF] expressed in ml. of 0·1057N-$Th(NO_3)_4$ per 5-ml. sample.

t (min.)	0	31	48	60	73	92	108	122	141	
[C_6H_5·COF]	2·17	1·85	1·69	1·61	1·52	1·40	1·29	1·18	1·07	
10^3k_0	—	4·67	4·85	4·73	4·68	4·60	4·70	4·87	4·91	Mean 4·75

The effect of solvent is shown in Fig. 1, from which it is observed that the rate of solvolysis is proportional to the cube of the water content, expressed as moles/l. of solvent, except in the most aqueous solutions. This effect is greater than for the S_N2

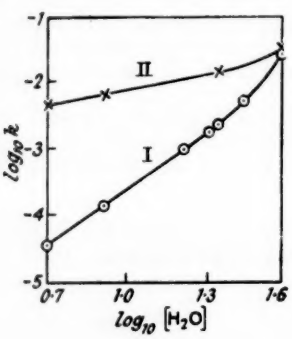

FIG. 1. *Relation between velocity constant at* 30° *and water content of the medium expressed as mole/l.*
(I) *Solvolysis.*
(II) *Catalysis.*

hydrolysis of simple alkyl halides, and is probably determined by the greater solvation around the partially ionised fluorine atom in the transition state than around corresponding chlorides and bromides. The acid catalysis is seen to be much less dependent on water concentration, as shown by the values of k_H in Table 1. The rate increase is approximately proportional to the water content of the medium (Fig. 1).

These results, together with those of Bernstein and Miller, show that the hydrolyses of benzyl fluoride and benzoyl fluoride are catalysed by acids to a similar extent. It is known that the corresponding chlorides hydrolyse by very similar mechanisms, so the tendency for the halide atom to ionise is of the same order in the two cases. It is logical therefore to assume that acid affects the hydrolysis of benzoyl and benzyl fluorides in the same way, *i.e.*, in the electrophilic removal of the fluoride ion.

The rate of the solvolysis increases rapidly with water concentration, showing that the pseudo-ionic transition state is highly solvated by water molecules in a similar way to the benzoyl chlorides. On the other hand, the rate of the catalysed reaction increases relatively slowly with increase in water content, indicating that water does not participate in the solvation, and the reaction is probably an example of electrophilic catalysis in nucleophilic substitution (cf. Hughes, Ingold, *et al.*, *J.*, 1940, 925).

Finally, the rate figures given in Fig. 2 show that lithium chloride causes no increase in rate, so the catalysis is due to H^+ ions alone and, as in the case of the chloride, no salt effect can be detected.

Experimental.—Preparation of benzoyl fluoride. Ammonium fluoride (70 g.), dried by azeotropic distillation with carbon tetrachloride, was added to acetone (250 ml.) which had been dried by refluxing it with potassium carbonate followed by distillation. Benzoyl chloride (110 ml.) was added slowly to the stirred mixture in an apparatus protected from atmospheric moisture, and the reagents were refluxed for 2 hr. on a water-bath. On cooling, the salt was rapidly filtered off and after removal of the acetone the benzoyl fluoride was distilled at reduced pressure

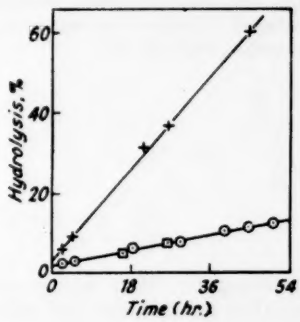

FIG. 2.

+ *In presence of* 0·05N-HCl.
⊙ *Pure solvent.*
⊡ *In presence of* 0·10N-LiCl.

and a middle fraction collected (b. p. 55°/18 mm.) (quantitative hydrolysis gave F, 15·2. Calc. for $C_6H_5{\cdot}COF$: F, 15·4%).

Rate measurement. This was done by titration of the liberated fluoride ion with thorium nitrate, sodium alizarinsulphonate being used as indicator. In a typical experiment 100 ml. of the solvent (made up by volume from pure dry acetone and distilled water) contained in a "Polythene" vessel were placed in the thermostat for an hour, after which 0·3 ml. of benzoyl fluoride was added, and the vessel rapidly shaken. 5-Ml. portions were withdrawn at appropriate intervals and added to 1 ml. of chloroacetic–chloroacetate buffer and 1 ml. of the indicator (0·1%). Infinity readings were obtained as the mean of a number of aliquots which had been at the thermostat temperature for at least ten times the half life.

The work on which this paper is based was carried out at the Chemical Defence Experimental Establishment, Ministry of Supply, Porton. The authors thank the Chief Superintendent of the Establishment and Mr. L. T. D. Williams for their hospitality.

QUEEN MARY COLLEGE, LONDON, E.1. [*Received, March 6th,* 1953.]

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452. *Steroids. Part XLVI.* Synthesis of* 11β-*Hydroxytestosterone and* 11-*Ketotestosterone.*

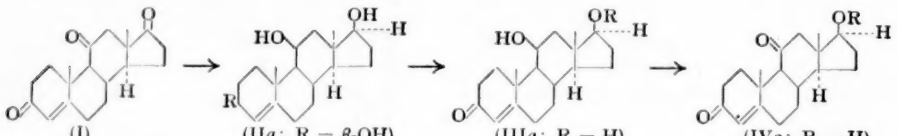
By O. MANCERA, G. ROSENKRANZ, and F. SONDHEIMER.

IN view of the remarkable pharmaceutical properties of 17α : 21-dihydroxypregn-4-ene-3 : 11 : 20-trione (cortisone, Kendall's Compound E) and 11β : 17α : 21-trihydroxypregn-4-ene-3 : 20-dione (hydrocortisone, Kendall's Compound F), it became of interest to make available for biological testing other and simpler 11-keto- and 11β-hydroxy-hormone analogues. We now report the synthesis of 11β : 17β-dihydroxyandrost-4-en-3-one (11β-

* Part XLV, Djerassi, Mancera, Romo, and Rosenkranz, *J. Amer. Chem. Soc.*, in the press.

hydroxytestosterone) (III*a*) and 17β-hydroxyandrost-4-ene-3 : 11-dione (11-ketotestosterone) (IV*a*) * from androst-4-ene-3 : 11 : 17-trione (adrenosterone) (I).

Adrenosterone (I) on reduction with lithium aluminium hydride yielded a mixture of, essentially, androst-4-ene-3β : 11β : 17β-triol (II*a*) and -3α : 11β : 17β-triol (II*b*) (for the stereochemistry of lithium aluminium hydride reduction of Δ^4-3-ketones 11-ketones, and 17-ketones see, *inter al.*, Dauben, Micheli, and Eastham, *J. Amer. Chem. Soc.*, 1952, **74**, 3852; Sarett, Feurer, and Folkers, *ibid.*, 1951, **73**, 1777; Rosenkranz, Kaufmann, and Romo, *ibid.*, 1949, **71**, 3689, respectively), which was oxidised directly with manganese dioxide in chloroform at room temperature. Only the allylic alcohol function was attacked under these conditions, and 11β-hydroxytestosterone (III*a*), further characterised as the 17-monoacetate (III*b*), was isolated in 62% overall yield. This transformation is analogous to that of androst-4-ene-3 : 17-dione to testosterone described recently (Sondheimer and Rosenkranz, *Experientia*, 1953, **9**, 62).



11-Ketotestosterone (IV*a*) was prepared simply and in excellent yield from the monoacetate (III*b*) by oxidation and subsequent hydrolysis.

Experimental.—Rotations were determined in chloroform, and ultra-violet absorption spectra in 95% ethanol solution.

Manganese dioxide. Concentrated aqueous potassium permanganate was added to a stirred aqueous manganese sulphate solution kept at 90°, until a slight excess was present (pink coloration of the supernatant liquid). Stirring at 90° was continued for a further 15 min. The oxide was collected by filtration, washed well with hot water, then with methanol and ether, and dried at 120—130° to constant weight. It could be kept for several months in a well-stoppered bottle without loss in activity.

11β : 17β-*Dihydroxyandrost-4-en-3-one* (11β-*hydroxytestosterone*) (III*a*). A solution of adrenosterone (350 mg.; m. p. 213—215°) in dry tetrahydrofuran (30 c.c.) was added dropwise to lithium aluminium hydride (300 mg.) dissolved in tetrahydrofuran (20 c.c.), and the mixture was heated under reflux for 30 min. The excess of reagent was decomposed by ethyl acetate, and a saturated aqueous sodium sulphate solution then added (until the precipitate began to adhere to the sides of the flask), followed by solid sodium sulphate (5 g.). The precipitated salts were removed and washed with tetrahydrofuran, and the filtrate was evaporated to dryness. The amorphous residue (350 mg.), dissolved in dry chloroform (35 c.c.), was shaken with manganese dioxide (3·5 g.) for 65 hr. at room temperature (*ca.* 20°). The oxide was removed and washed well with hot chloroform. Evaporation, chromatographic purification of the residue on alumina, and crystallisation of the fractions eluted with chloroform from acetone–hexane then furnished the 11β : 17β-*dihydroxy*-compound (220 mg., 62%), m. p. 228—232°. Further crystallisation yielded a sample, m. p. 232—234°, $[\alpha]_D^{20}$ +155° (Found : C, 74·85; H, 9·45. $C_{19}H_{28}O_3$ requires C, 74·95; H, 9·25%). Light absorption : Max. 2420 Å, $\varepsilon = 16{,}600$.

Acetylation (pyridine–acetic anhydride, room temp., 16 hr.) furnished the 17-*acetate* (III*b*), plates (from ether–hexane), m. p. 149—150°, $[\alpha]_D^{20}$ +123° (Found : C, 72·9; H, 8·85. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·75%).

17β-*Hydroxyandrost-4-ene-3* : 11-*dione* (11-*ketotestosterone*) (IV*a*). 11β-Hydroxytestosterone 17-acetate (100 mg.) in glacial acetic acid (3 c.c.) was oxidised with chromium trioxide (50 mg.) in 80% aqueous acetic acid (1 c.c.) for 30 min. at room temperature. Crystallisation of the product from acetone–hexane yielded the 17-*acetate* (91 mg., 92%) of (IV*a*) as long needles, m. p. 162—163°, $[\alpha]_D^{20}$ +170° (Found : C, 73·2; H, 8·5. $C_{21}H_{28}O_4$ requires C, 73·25; H, 8·2%).

This product was hydrolysed by refluxing it for 30 min. with potassium carbonate in aqueous

* While this manuscript was in preparation, independent and different syntheses of (IV*a*) were reported by Herzog, Jevnik, Perlman, Nobile, and Hershberg (*J. Amer. Chem. Soc.*, 1953, **75**, 266).

methanol. The resulting keto-alcohol, produced in nearly quantitative yield, crystallised from acetone–hexane as felted needles, m. p. 183—184°, $[\alpha]_D^{20}$ +210° (Found: C, 75·6; H, 8·7. Calc. for $C_{19}H_{26}O_3$: C, 75·45; H, 8·65%). Light absorption: Max. 2380 Å, ε = 16,200 {Herzog *et al.* (*loc. cit.*) give m. p. 181—182·4°, $[\alpha]_D^{25}$ +178° (in $COMe_2$); light absorption: Max. 2380 Å, ε = 14,400}.

Thanks are offered to Srta. Paquita Revaque for the ultra-violet light absorption data and to Srta. Amparo Barba for the microanalyses.

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[*Received, March 10th,* 1953.

OBITUARY NOTICE.

J. L. A. MACDONALD.

1887—1952.

On December 20th, 1952, Dr. J. L. A. Macdonald, D.S.O., D.Sc., for many years Chief Chemist to the paper-making firm of Tullis Russell, died suddenly at his home, Cadham House, Markinch, Fife.

James Leslie Auld Macdonald was born on March 27th, 1887, at 1, Leigham Court Road, Streatham, London. He was the only son of Thomas Macdonald, Barrister-at-Law of the Middle Temple. Leslie, as he was known to his friends, was educated at Rugby School and at St. Andrews University, where he graduated B.Sc., with honours in Chemistry, Geology, and Zoology, in 1909.

Inspired by the teaching of Professors Purdie and Irvine, Macdonald took up research in Chemistry, and until 1914 he held a Carnegie Fellowship at St. Andrews. During this period he worked on various reactions of glucose and acetone, and his results, partly in his own name and partly in collaboration with Professor J. C. Irvine, were published in the *Transactions of the Chemical Society*.

During the First World War he served with the infantry in France, was awarded the D.S.O., and attained the rank of Lt.-Col., commanding the 12th (S.) Bn. the Royal Scots.

On demobilisation he returned to St. Andrews University, where in 1919 he was awarded the D.Sc. degree for his thesis on the acetone derivatives of reducing sugars. In the autumn of the same year he became Chief Chemist to the firm of Tullis Russell at Markinch, a post which he held until his retirement in July 1952. Under his guidance the laboratories were much enlarged and the scope of the laboratory work greatly extended. Among the varied researches directed by him during this period was the differential staining of paper-making fibres which is so admirably illustrated in the monograph produced by the Company in 1950. He was a member of the first Committee of the Technical Section of the Paper Makers' Association of Great Britain and Ireland, and he took a prominent part for many years in its proceedings. In recent years most of his practical laboratory work had been devoted to the study of alternating currents of very high frequency; though he had made some interesting observations the results were not yet sufficiently coherent to warrant publication.

Dr. Macdonald had for many years been President of the Markinch Branch of the British Legion. During the Second World War he was Commanding Officer of the 5th Fife Bn. of the Home Guard from its inception, and in 1943 he was promoted to the rank of Colonel and given command of the South Fife Sector.

As a young man he was a very pretty golfer, capable of completing the Old Course at St. Andrews in less than 80, and he still retained his membership of the Royal and Ancient Golf Club. He was a skilled photographer, a keen horticulturalist, and an expert fly-fisherman. In all these activities he excelled through the application of scientific method.

Dr. Macdonald is survived by his wife, one son, and one daughter.

E. W. Shann.

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